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A CIRCULATORY STUDY AT REST, SUBMAXIMAL AND MAXIMAL LEVELS OF EXERCISE BEFORE AND AFTER THE INFUSION OF LOW MOLECULAR WEIGHT DEXTRAN

by

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APPROVAL SHEET

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "A Circulatory Study at Rest, Submaximum and Maximum Levels of Exercise Before and After the Infusion of Low Molecular Weight Dextran", submitted by Allan R. McClelland in partial fulfillment of the requirements for the Degree of Master of Science (Medicine).

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October, 1968,

Allan R. McClelland

ABSTRACT I

CHANGES IN MAXIMUM CARDIAC OUTPUT DURING EXERCISE

AFTER INFUSION OF LOW MOLECULAR WEIGHT DEXTRAN

Cardiac output (C.O.) during maximal exercise may be limited by the venous return to the heart or the pumping capacity of the ventricles. In a preliminary study carried out on five normal subjects by measuring the maximum cardiac output before and after the infusion of one liter of autologous blood, no significant change in maximum cardiac output was found following the transfusion. From this experiment it was concluded that the venous return was not the limiting factor of maximum cardiac output. Therefore, the pumping capacity of the heart must be the factor that limits cardiac output.

In the present investigation, twelve normal male subjects were studied before and after infusion of Dextran (1 liter), at rest, and at maximal exercise. Heart rate (H.R.), oxygen uptake ($\dot{V}O_2$), and right atrial pressure ($\bar{R.A.p}$) were measured, but no significant change in these parameters was found following the infusion of Dextran. Cardiac output, central blood volume (C.B.V.), and stroke volume (S.V.), increased after Dextran infusion both at rest and at exercise. Maximal cardiac output changed from 18.2 l/min. in the preinfusion study to 22.3 l/min. in the postinfusion study. Stroke volume changed from 97 to 120 mls, and the C.B.V. from 1000 mls. to 1200 mls. Systemic vascular resistance (S.V.R.), Hct., and viscosity dropped significantly (20%, 12% and 10% respectively) following Dextran infusion.

This change in maximum C.O. following Dextran infusion was attributed to the decrease in S.V.R. resulting from the decrease in blood viscosity. The limiting factor of maximum C.O. is therefore the capacity of the heart, as the maximum C.O. can be increased with reduced afterload (i.e. the tension that the ventricles are called upon to develop during contraction) but not with an increase in the venous return alone.

ABSTRACT II

CHANGES IN SELECTED CIRCULATORY AND PULMONARY PARAMETERS DURING VARIOUS INTENSITIES OF EXERCISE UP TO THE MAXIMUM

Exercise is widely used as a means of studying abnormal cardio-respiratory functions in patients, although there is insufficient data available on normal individuals. In this study, cardiovascular and respiratory parameters were measured at rest, during three levels of submaximal exercise (25%, 50%, and 75% of maximum $\dot{V}O_2$), and at maximal exercise in order to study these changes as a function of exercise intensity.

In twelve normal male subjects, cardiac output (C.O.) and central blood volume (C.B.V.), (using cardio-green dye), heart rate (H.R.), oxygen consumption ($\dot{V}O_2$), respiratory quotient (R.Q.), arterial O_2 content, arterial pO_2, pCO_2, and pH, arterial lactate, aortic pressure (Art.$\bar{p}$), and right atrial pressure (R.A.$\bar{p}$) were measured at rest and during exercise on a Bicycle Ergometer. Some of the data obtained is listed below:

		REST	25%	50%	75%	MAX.
$\dot{V}E$	l/min.	10 ± 2	20 ± 4	38 ± 9	61 ± 13	99 ± 18
$\dot{V}O_2$	l/min.	.34 ± .04	.84 ± .17	1.7 ± .30	2.56 ± .40	3.24 ± .41
C.O.	l/min.	6.1 ± 1.4	10.1 ± 2.1	14.4 ± 2.6	17.7 ± 3.3	18.6 ± 3.6
R.A.$\bar{p}$	mm Hg.	0.5 ± 2.6	1.9 ± 1.9	2.3 ± 1.3	2.7 ± 2.2	5.4 ± 4.1
Art.$\bar{p}$	mm Hg.	109 ± 14	126 ± 19	126 ± 19	152 ± 20	156 ± 19

During exercise, C.O. increased linearly with $\dot{V}O_2$ up to 75% of maximum exercise and then levelled off. Stroke volume (S.V.) reached

a maximum at 50% and 75% of maximal exercise and then fell during the maximal exercise. R.A.$\bar{p}$ increased sharply during maximal exercise which may account for the fall in S.V. The ratio of $\dot{V}E/\dot{V}O_2$ increased steeply along with a fall in pCO_2 during maximal exercise indicating disproportionate hyperventilation had occurred at this level. PO_2 decreased slightly during 75% and 100% of maximum exercise, and pH fell progressively as the lactate content of the blood increased during these two work levels. The C.B.V. increased from 640 mls. at rest to 980 mls. at the 75% level, but no further increase was noted at maximum exercise suggesting that maximal dilatation of the pulmonary vascular bed had occurred at this level.

ABSTRACT III

STROKE VOLUME AS A FUNCTION OF HEART RATE AND VENTRICULAR FILLING PRESSURE AT REST AND DURING VARIOUS INTENSITIES OF EXERCISE

The relationship between stroke volume (S.V.) and other cardiovascular parameters has not been clearly established, particularly in the region of maximal exertion.

In this investigation cardiac output (C.O.), heart rate (H.R.), right atrial pressure (R.A.$\bar{p}$), oxygen uptake ($\dot{V}O_2$) and S.V. were studied in twelve normal subjects at rest, three levels of submaximal exercise (25%, 50%, and 75% of maximum $\dot{V}O_2$) and maximal exercise on a bicycle ergometer. Some of the results are as follows:

		REST	25%	50%	75%	MAX.
H.R.	/min.	80 ± 14	101 ± 14	131 ± 12	164 ± 11	189 ± 8
R.A.$\bar{p}$	mm Hg.	1.1 ± 2.4	2.0 ± 1.7	2.2 ± 1.2	3.0 ± 1.7	4.9 ± 2.1
S.V.	mls.	75 ± 23	99 ± 23	108 ± 26	108 ± 25	97 ± 24

Stroke volume was a maximum at 50% and 75% of maximal exercise but showed a distinct fall during maximum exertion. This was accompanied by a significant rise in heart rate and the right atrial pressure. The stroke volume was found to be a parabolic function of both R.A.$\bar{p}$ and H.R.: $S.V. = -6.1(R.A.\bar{p})^2 + 39(R.A.\bar{p}) + 45.5$ and $400S.V. = -2.95(H.R.)^2 + 838(H.R.) - 15484$. It was found that the optimum H.R. and R.A.$\bar{p}$ were reached at about 75% of maximum exercise and a further increase in these parameters during maximum exercise reduced stroke volume.

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INTRODUCTION

The maximal cardiac output of normal individuals and athletes has been studied using bicycle ergometer[2,5] or treadmill[7,8,51] exercise. This maximal pumping capacity of the heart, which has been accepted as the limiting factor of maximal exertion (maximum oxygen uptake), has been found to be related to the cardiovascular parameters such as dimensions of the heart, blood vessels and working muscle mass, total circulating hemoglobin and blood volume, and has been found to increase with physical training. However, the control of this maximum capacity has not been clearly evaluated.

The limiting factor of maximum cardiac output could be either the capacity of the heart as a pumping chamber, or the maximum venous return. In an attempt to determine the significance of the latter, Robinson et al.[55] studied maximum cardiac output before and after blood transfusion and concluded that "an acute increase in blood volume and central venous pressure does not result in any increase in the response of cardiac output to maximal exertion", and consequently, "that the blood volume and central venous pressure are not the factors which limit the cardiac response to exercise in normal subjects."

In order to confirm the findings of Robinson et al.[55] a preliminary study was carried out on five normal subjects by measuring the maximum cardiac output before and after the infusion of one liter of autologous blood, which had been withdrawn two weeks prior to the

experiment. No significant changes in the maximum cardiac output were found following transfusion, confirming the conclusion of Robinson et al.[55] From these observations it was concluded that the venous return was not the limiting factor of maximum cardiac output.

The pumping capacity of the heart must then be the factor that limits cardiac output. The provision of evidence for this statement stimulated the research for this thesis.

The evaluation was carried out by studying the effects of exercise on the circulatory parameters of twelve normal males before and after the infusion of low molecular weight dextran. Others have shown the effect an expanded blood volume has on resting circulatory parameters, but no one has attempted to show the effects during submaximal exercise.[31,32,42,47,53,55]

Another purpose of this study was to examine various circulatory changes at different levels of submaximal and maximal exercise.

STATEMENT OF THE PROBLEM

I THE PRINCIPLE PROBLEM

The prime purpose of this study was to ascertain whether maximum cardiac output could be increased further by infusion of low molecular weight dextran. The aim was to provide further evidence as to the extent the pumping capacity of the heart plays in limiting cardiac output.

II THE SUBSIDIARY PROBLEMS

(a) To evaluate the effects of an expanded blood volume on circulatory parameters such as central blood volume, right atrial pressure, arterial pressure, cardiac output, heart rate, stroke volume and blood gases during submaximum and maximum exercise.

(b) To study the circulatory changes as a function of the intensity of exercise.

BACKGROUND INFORMATION

Maximum cardiac output is the maximum pumping capacity of the heart stimulated by the metabolic demands of a large working muscle mass. The circulatory parameters responsible for meeting the increased body metabolism can be expressed algebraically according to Fick's equation: $\dot{V}O_2$ = H.R. x S.V. x A - V Difference. During maximal exertion (on a treadmill or bicycle ergometer), all of these values are reported to be at a maximum. The heart rate (H.R.), controlled by hormonal and sympathetic stimulation, shows a linear relationship with oxygen uptake ($\dot{V}O_2$) - both reaching their maximal values at about the same time.[3,51] Maximal heart rate varies with the age and physical fitness of the subject - being high in the young sedentary individuals, but decreases with age and physical fitness.[2,3,5,51] Rushmer[57,58] contends that heart rate controls cardiac output to a far greater extent than stroke volume (S.V.).

The other parameter in controlling cardiac output is the S.V. which is dependent upon a) myocardial contraction,

b) afterload, or the tension that the muscle is called upon to develop during contraction,

c) end-diastolic volume.[13]

The latter is controlled by three variables - i) the blood volume, ii) the diastolic filling time, and iii) the ventricular filling pressure which determines the length of the muscle fibers at the onset of contraction (i.e. the preload). A change in any of these five variables

will result in a change in stroke volume.

Starling,[64] in expressing his law of the heart, emphasized the importance of an increase in stroke volume to meet the demands for increased blood flow. Several other authors have shown that stroke volume increases markedly upon transfer from rest to work.[2,17,51,72] Astrand, et al.[6] using a bicycle ergometer and the dye-dilution technique for measuring cardiac output have found in males an average stroke volume at rest of 88 mls. and a maximum of 134 mls. during exercise. In these subjects maximal work was maintained for at least six minutes without any decrease in stroke volume. Saltin[59] has shown also that as cardiac output increased the stroke volume showed no significant change past a work level which was 40% of the aerobic capacity. The increase in cardiac output above this level was solely a function of the increased heart rate. However, it has not been clearly established whether or not there is an increase in the stroke volume contributing to an increase in cardiac output in the maximal region of exertion.

During exercise the contractile state of the myocardium is normally augmented by the sympathetic nerve impulses, concentration of circulating catecholamines and tachycardia.[14,48,57,58,60] It is depressed by hypoxia, hypercapnea and acidosis.[14]

The afterload is influenced largely by the peripherial vascular resistance, 29 the physical characteristics of the arterial tree and the volume of blood that it contains at the onset of ejection. These factors can be grouped as the aortic impedence which, if reduced to zero,

would result in almost complete ventricular emptying.

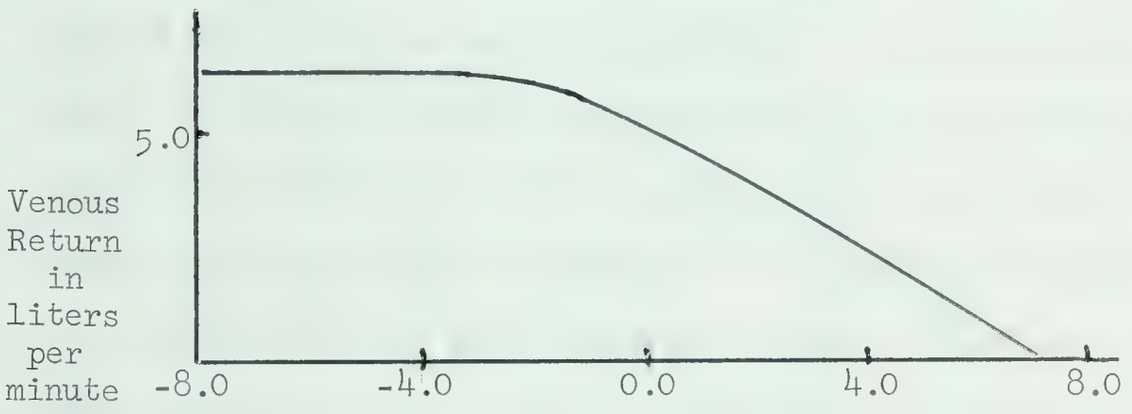
The end-diastolic volume profoundly influences the amount of blood ejected per beat no matter what the myocardial state. This parameter, which is a measure of the sarcomere length at the time of their activation, is determined by the volume of blood and its distribution. When blood volume is decreased (as in hemorrhage), ventricular stroke volume is decreased. The converse is also true. With exercise, the distribution of the blood volume changes such that the exercising muscles receive a far greater supply and the blood supply to other body areas is diminished (i.e. gut, kidney and spleen).

Holmgren[44] and Bevegard[10] have shown that the duration of mechanical systole of the ventricles varied as linear function of heart rate. "The slope of the decrease was such that a change in heart rate from 140 beats per minute to 170 beats per minute was accompanied by a decrease in the mechanical systole from 0.24 seconds to 0.20 seconds. At the same time, the mechanical diastole (i.e. the time available to fill the heart) is shortened from 0.21 seconds to 0.167 seconds".

Ventricular filling is also augmented by vigorous atrial contraction.[11,49] This is particularily important during exercise. Venous return will also determine the degree of ventricular filling. Like cardiac output, the venous return, can change from second to second, from minute to minute, or from one physiological state to another. This is shown in Guyton's venous return curve.[41]

Circulatory reflexes or autonomic drugs can shift the entire curve upward or downward.[39] Changes in blood volume can do the same.[40]

Also, alterations in peripheral-vascular resistance can cause the downslope of the venous return curve to change markedly, decreased resistance causing the slope to become greater and increased resistance causing the slope to become less.[41]



A normal venous return curve extrapolated to the human being. (From Guyton's Circulatory Physiology, page 186.)

Thus, since venous return is readily altered by extracardiac parameters it has been considered the major factor in determining maximal cardiac output by setting the limit on ventricular filling when the ventricles may still be capable of augmenting their performance. One way of augmenting venous return is to increase total blood volume upon which many investigators fell that the maximum circulatory response is dependent. However, the evidence for this is indirect.[46,66,67] Danzinger and Cumming[22] studied the effect of a deliberate reduction of blood volume induced with chlorothiazide and found that maximum oxygen was consistently lowered. They showed this change could be reversed with intravenous dextran. The effects of deliberately augmenting the blood volume was studied by Gull-

bring, et al.[38] who infused a quantity of the subjects own blood and found that the heart rate was lower at any given work level compared with that found in a preinfusion study. From these experiments, they concluded that the working capacity had increased. However, they did not measure cardiac output and oxygen uptake. The latter was done by Robinson, et al.[55] who found an augmentation of blood volume produced a substantial increase in cardiac output in the upright position at rest. However, the output during maximal exertion was not increased despite a considerably higher central venous pressure. They found that maximum oxygen uptake did not rise following blood transfusion, and that cardiac output was not increased. The possibility that the work load after infusion was of insufficient magnitude to evoke a maximum cardiac output response was excluded by the large oxygen debt which was accumulated in each case. Thus, the cardiac output failed to achieve a higher level during maximal exercise after expansion of blood, despite the fact that the level of output was inadequate to meet the metabolic needs. The reasons for this inability of the heart to augment its performance during exercise in spite of an elevation of central venous pressure may be attributed to a number of specific mechanisms. Firstly, it is possible that the "right ventricle is operating at the peak or on a flat portion of its function curve, in which case a rise in central venous pressure, although associated with an increased end-diastolic fiber length, would not further augment cardiac output."[55] Secondly, it is possible that the "elevation of central venous pressure is not

associated with an increase in end-diastolic fiber length during maximum exercise".[55] The duration of diastole is very brief at rapid heart rates and it is possible that the abbreviation of diastole during tachycardia may result in insufficient time for the ventricle to relax completely. As seen from Guyton's venous return curve,[42] an elevation of central venous pressure would tend to decrease venous return to the right atrium. Thus, it becomes apparent that not one, but many factors acting together must set the limit of cardiac output.

It is generally accepted that the capacity for exercise using large muscle groups (as in running or bicycling) depends on the oxygen transport system. In normal individuals with no respiratory problems the maximum $\dot{V}O_2$ depends on the maximum cardiac output.

Atmospheric oxygen reaches the exercising muscles only by the circulatory system. Also, the increase in acid load (CO_2 and lactic acid) during exercise requires the ventilation rate to be synchronized with the production of these end products - minimizing changes in the arterial pH[73]. There exists, therefore, a relation between muscle perfusion and oxygen demand, this relationship being linear in the submaximal regions but reaching a plateau at maximal exercise. Donald and his colleagues [26] and others[54,35] have clearly demonstrated this highly predictable relationship between cardiac output and the oxygen consumption of exercise in normals. Divergences from this normal response have been demonstrated in a variety of circulatory diseases.[12] Astrand [4,5,6] and Taylor, et al.[69] have found that there are some subjects who do not show a clear cut plateau, but all subjects show a falling off from the linear rise observed in the submaximal levels

of exercise. Wyndham et al.[77] have clearly shown that the maximum oxygen uptake is approached asymptotically, but twenty to twenty-five determinations of oxygen consumptions versus work load are necessary for each subject to determine the point at which the straight line relationship no longer holds. These authors concluded that the maximum $\dot{V}O_2$ obtained by the method of Taylor et al.[69] could lead to an underestimation. However, because the method of Wyndham[77] is very time consuming, a modified method of Astrand[5,6] was used in this study.

Dill[25] and Robinson[56] determined maximum $\dot{V}O_2$ by having the subject run on a motor-driven treadmill at a rate which would exhaust him in five minutes. Astrand[6] used a post-exercise concentration of lactic acid in the blood of 100 mgm./100 mls. of blood as a criterion for maximal exertion.

Whatever the method used to determine the point of maximum oxygen uptake, a point is reached, as Hill predicted, beyond which further increases in work load fail to increase the oxygen intake. At this point the cardiac output is maximal, A - V Difference is close to maximum and lactic acid build-up approaches a maximum.

Maximum oxygen uptake depends mainly on the amount of skeletal muscle and the ability of the cardiovascular system to perfuse the working muscles with oxygenated blood.[20,24] Other relevant attributes are the ventilatory and gas transfer properties of the lungs, and the total amount of hemoglobin. Maximum $\dot{V}O_2$ therefore, measures the combined capacity of the cardiovascular system to transport oxygen, and of the working muscle to utilize oxygen.

Many procedures are available for assessing an individual's maximum oxygen capacity, but only four are in general use. These direct tests include:

a) Intermittent treadmill[51,56,58]

b) Continuous treadmill [7,8]

c) Bicycle ergometer[2,5]

d) Step test[19]

In each of these tests it is generally agreed that a warm-up requiring a $\dot{V}O_2$ of 40% to 50% of the maximal oxygen uptake will increase the maximum oxygen uptake by 5%. Thus, a warm-up becomes an integral part of the testing procedure.

Several investigators have evaluated the above tests, concluding that the intermittent treadmill test is the most accurate.[36, 52,76] The results from a bicycle ergometer test are similar to those of the intermittent treadmill test at the low levels of exercise, but at higher levels of exercise the results become significantly lower.[76] The reason for this may be that in bicycling the body weight is not supported by the legs.[15] Astrand and Saltin[4] point out that bicycling requires additional muscular development and training. However, these authors conclude that maximum oxygen uptake values can be compared with precision from one laboratory to another. Investigators working in different laboratories obtain results in the test-retest situation which have a standard deviation of the same order of magnitude. Astrand and Saltin[4] normalized the data by obtaining the difference between the highest value for any one person and the mean percent for all subjects

studied, and then calculated the standard deviation. "This resulted in a standard deviation of 3.15% in the study of Astrand and Saltin[3], 3.0% in that of Mitchell et al.[51] and 2.8% in that of Taylor et al."[68]

The length of time used to attain steady state cardiovascular and respiratory parameters varies with different investigators. Mitchell et al.[51] used a ten minute warm-up on a treadmill at 3 miles per hour and at 10% grade, followed by a $2\frac{1}{2}$ minute run at six miles per hour and 0% grade. Data presented by Taylor, Buskirk and Henschel,[68] Robinson,[56] and Donald, Bishop, Cumming and Wade[26] suggest $2\frac{1}{2}$ minutes are adequate in obtaining a steady state. After a ten minute rest, the load was increased by raising the treadmill grade 2.5%. This sequence continued until maximal $\dot{V}O_2$ was obtained. Astrand and Saltin[4] exercise their subjects on a bicycle ergometer at a pedaling frequency of 50 pedal turns per minute. The subject starts at a light submaximal load for 6 minutes, followed by a 5 minute rest. The cardiovascular and respiratory parameters are measured during the 5th and 6th minutes of exercise. The subject again exercises for 6 minutes at a higher work load followed by a 5 minute rest. This sequence continues until maximal oxygen uptake is attained. At maximal work the pedal frequency was increased to 60 or 70 turns per minute.

In the present study, the subject's maximal $\dot{V}O_2$ was determined prior to the experiment day and the submaximal work levels were chosen to give uptake values of approximately 25%, 50% and 75% of the maximal $\dot{V}O_2$. These three submaximal levels of work were completed in a continuous sequence of 6 minutes, 4 minutes and 4 minutes respectively, followed

by a fifteen minute rest. Prior to maximal exertion the subject exercised at the 50% level for 6 minutes and then went directly into the maximum for 4 minutes. All work was done on a bicycle ergometer.

Other cardiovascular parameters which change with exercise are the hemoglobin and hematocrit, both of which tend to increase with exercise. The pO_2, pCO_2 and pH also change, there being a slight decrease in pO_2 and pH and an increase in pCO_2 as maximal cardiac output is approached. Systemic and right atrial pressures all increase with increasing work load. Arteriovenous oxygen difference increases with increasing oxygen uptake all the way from rest to maximal exercise. From a large number of experiments, Wade and Bishop[71] concluded that the oxygen uptake and A - V Difference are related by a hyperbolic function. This was also pointed out by Ekelund and Holmgren.[27]

In this study blood volume was increased with 6% dextran which is a polysaccharide of glucose residues in an α, 1-6 linkage - much like cellulose, starch and glycogen - which is polymerized from sucrose by various strains of bacterium Leuconostoc Mesenteroides. Partial acid hydrolysis and fractionation provide a low molecular weight dextran (molecular weight of 40,000) of relatively uniform viscosity (0.09 intrinsic viscosity). Dextran is currently being used for clinical and experimental studies to:

a) alter erythrocyte sludging,

b) reduce blood viscosity in four ways:

i) Plasma - volume expansion

ii) Formation of dextran-fibrinogen complex

iii) Alteration of erythrocyte surface charge.

iv) Siliconizing effect on injured walls of blood vessels.[1,18,21,61,62,63,70,74]

Low molecular weight dextran is excreted slowly from the body: 55% within the first four hours and 60% - 90% within twelve hours.[23,30] Prather et al. have shown 90% retention of the infused volume of dextran after one hour and 50% retention of infused volume of whole blood.[53]

A small number of dextran molecules will equilibrate in the extra vascular compartment as the renal threshold for dextran is 50,000. After a few days it will be metabolized to CO_2 and H_2O.[30]

Dextran has other effects on the circulation which are capable of altering the cardiac output. It first causes a relative anemia, by lowering the hematocrit. This lowers the viscosity of the blood which in turn tends to decrease the resistance of venous return and decreases the resistance load on the heart.[42] The latter effect alone is capable of increasing the cardiac output up to 30%. There is also increased vasodilation and reflex stimulation of the circulation through the chemoreceptor mechanism resulting from relative anemia.

Thus, with the mild anemia produced by dextran, the cardiac output should be increased even at the maximal levels. Some evidence has already been obtained pertaining to the effect of dextran on circulation. Fowler et al.[31] and Witham et al.[75] were able to increase the cardiac output in resting man with the infusion of 500 mls. of 6% dextran and in anesthetized dogs with the infusion of 80 mls. per kilogram. This rise in cardiac output was not dependent upon the augmentation of blood volume, since cardiac output performance was essentially

unchanged when a comparable expansion of blood volume was produced by the infusion of whole blood.[32,53,55,47] Fowler et al.[31] demonstrated that the production of anemia by dextran exchange could increase cardiac output even though the blood volume had been reduced to normal, and that increased filling pressure in the right heart was not essential for this response.[33] This indicates that anemia with the resulting decrease in arteriovenous difference plays a part in increasing cardiac output. Gowdey[37] has shown that anemia does not cause an increase in cardiac output by the action of catecholamines or of sympathetic nerves upon the heart. Fowler[34] later showed that "in dog heart-lung preparations, a one liter dextran exchange lowered hematocrit from an average of 53 to 13, with an average increase in cardiac output of 38%, and an in vitro decrease in blood viscosity of 33%. Atrial pressures fell and ventricular force rose. When blood viscosity was reduced without anemia by an exchange of dog red cells suspended in Kreb's solution, there was a similar change in cardiac dynamics. These results suggest that reduced blood viscosity is an important factor in the increased cardiac output of anemia."

It has been established that normally circulation is the limiting factor in exercise and that peripheral and cardiac factors play almost equal roles in determining cardiac output.[29,45] However, when the heart is working at maximum (during maximum oxygen uptake), the cardiac factors become constant, and it appears that any change in the cardiac output (especially an increase) must result from a change in the

peripheral resistance.[29] This resistance can be lowered by reducing the viscosity of the circulating blood or increasing the peripheral vascular radius.

METHODS AND PROCEDURES

This study was completed in three units:

a) A preliminary study to determine the work load for the main study.

b) Preinfusion study to determine the cardiovascular and respiratory adaptions to four levels of exercise.

c) Postinfusion study to determine the same parameters after the blood volume has been expanded with 1000 c.c. of 6% dextran.

The subjects for this study were healthy male students and personnel of the University of Alberta Hospital. Half of them were engaged in active sports while many of the remaining half had been active or were active in their jobs.

The preliminary studies for each of the twelve subjects involved a minimum of sixteen $\dot{V}O_2$ versus work load determinations requiring from four to seven days. On any one day the subject would exercise on the Fleisch bicycle ergometer at four increasing work loads. The first load - for six minutes - was the lightest (usually 25% of the maximum exercise level set for that day) followed by two increasing work loads (50% and 75% of that days maximum) for four minutes each. The subject then rested for fifteen minutes. A six minute warm-up followed at the 50% work level set for that day followed by four minutes of exercise at the heaviest load. These determinations were continued until a linear $\dot{V}O_2$ versus work load relationship was obtained in the submaximal region

and a plateau in the maximal region - see figure 1 as an example. Many investigators agree that four minutes of exercise after a warm-up is enough for the body to attain a steady state condition.

Expired air was collected in Douglas bags during the last thirty seconds of each work load. Heart rate was obtained from an E.K.G., recorded the last ten seconds of each exercising minute.

From the $\dot{V}O_2$ vs. work load graph the maximum work load and $\dot{V}O_2$ were taken at the beginning of the plateau. The submaximal work loads were obtained from the graph corresponding to 25%, 50% and 75% values of the maximum oxygen uptake. It was these four work levels determined in this manner that were used on the experimental day.

The preliminary studies also acquainted the subject with the procedure and much of the equipment used on the experimental day. The preliminary results are summarized in table VIIa and VIIb.

On the experimental day, each subject arrived at the hospital after a light breakfast. After changing into a light pair of pants, the subject went to the catheterization room. Under local anaesthetic, a 0.034" teflon catheter was introduced percutaneously by the Seldinger technique into the right brachial artery and positioned in the ascending aorta about two inches above the valve. A 6 French Raycatheter was introduced into the right antecubital vein using a cut-down procedure, and positioned in the right atrium. Fluoroscopy was used in the positioning of both catheters.

The subject then walked a short distance to the exercise

laboratory and was seated on the Fleisch bicycle ergometer. The arterial and venous catheters were connected to P23Db Statham physiological transducers as shown in figure 2. These were then positioned level with the right atrium. The arterial and venous pressures and E.K.G. were recorded on an eight channel Beckman Dynograph R Recorder. A Beckman E.K.G. cable was used with the L.A. lead at the apex of the heart, the R.A. lead over the apex of the scapula and the R.L. lead on the forehead.

A Harvard infusion-withdrawl pump with a 30 c.c. luer-lock siliconized syringe was used to withdraw blood at 14.8 c.c./minute from the aortic catheter through the Waters X 301 cuvette. No blood was reinfused. A Waters XP 302 Densitometer with the Beckman R Recorder was used to record the dye curves. About 1.3 mls. of Indocyanine Green (Hyson,Westcott and Dunning, Baltimore, Md.) in a concentration of approximately 3.3 mgm/ml (the exact volume injected and concentration of dye was obtained by weight determination) was injected from a two c.c. B.D. spring-loaded syringe into the right atrium.

Expired air was collected in Douglas Bags connected by 1.5" corrugated tubing to a high velocity one-way Collins valve held in position by a head harness. The tubing was flushed with the subjects' expired air prior to each collection. The resistance to flow of this gas collection system - shown in figure 3 - is shown in figure 5. The oxygen content of the expired air was determined by an E-2 Beckman analyser - CO_2

by a Godart Capnograph. At least three determinations were made on each gas sample and then averaged. Both instruments were calibrated twice a day with chemically analyzed gas. The volumes were measured by a gasometer (American Meter Company) which was calibrated against a Collins Spirometer. Expired air was collected at rest, during the last thirty seconds of each submaximal work load and during the last thirty seconds of every minute during the four minutes of maximal load.

Blood was collected in ten c.c. heparinized syringes at rest and at the end of each exercise level and immediately put into the refrigerator. This was later used to determine the capacity on a Van Slyke instrument and the pCO_2, pO_2 and pH on an Instrumentation Laboratories blood gas analyser. Six c.c. of blood were also collected in a similar sequence and divided into two cold centrifuge tubes containing five c.c. of Tricholoracetic acid. These were later analyzed for lactic acid using the method of Ellis, Cain and Williams.[28] The absorption was measured on a Beckman DU Spectrophotometer.

The arterial catheter was frequently flushed with heparinized saline to keep it from clotting. The venous catheter always remained filled with cardio-green dye.

After obtaining the resting blood samples, expired air, pressures, heart rate, and cardiac output, the subject began exercising at the 25% $\dot{V}O_2$ level. Heart rate and pressure were recorded at the end of every minute. A cardiac output was obtained at the end of the fifth and sixth minutes. Expired air was collected the last thirty seconds of the

sixth minute. Blood samples were obtained during the last ten seconds of the sixth minute. The second level of exercise (50% of max. $\dot{V}O_2$ level) was started at the beginning of the seventh minute and continued until the end of the tenth minute. The same sequence for obtaining cardiac output, expired air and blood was followed for the ninth and tenth minute. The 75% $\dot{V}O_2$ level of exercise began at the eleventh minute and ended at the fourteenth with a similar sequence of collections at the thirteenth and fourteenth minutes.

The subject then rested for fifteen minutes before starting the six minute warm-up set at 50% of the maximum $\dot{V}O_2$ work load. No parameters were measured during this period. On completion of the warm-up the subject went directly into the maximum load. Expired air was collected the last thirty seconds of each minute. Cardiac output was determined at the end of the second, third and fourth minutes. Pressures and heart rate were recorded every minute. The blood samples were obtained during and after the last ten seconds of the fourth minute. Exercise was stopped after four minutes.

The catheters were flushed with heparinized saline and disconnected from the transducers. The E.K.G. was uncoupled. The subject then lay on a stretcher for two hours during which time 1000 c.c. of six percent dextran was infused through the venous catheter. The subject also ingested fluids and a hamburger or sandwich.

At the end of the two hours the subject was again positioned on the Fleisch bicycle ergometer and the catheters connected to the

transducers. He again repeated the four levels of work and the same parameters were measured.

For the first six subjects, the Waters cuvette was calibrated after both the preinfusion and postinfusion study by the integrated sample technique.[50] Since there was no significant difference in the two curves, calibration was carried out at the end of the experiment for the last six subjects. End exercise blood was always used. Calibration of the pressure transducers was done at the end of the experiment with a mercury column.

The frequency response of the catheter - transducer system was not determined or compensated for. This may have lead to an error - particularily in the aortic pressure.- as heart rate approached a maximum. However, because each subject acted as his own control, the postinfusion frequency response may be different from the preinfusion response because of the change in viscosity due to the dextran infusion. It may not be valid, therefore, to compare the two studies as the measuring error would not be the same for each study.

The dye-dilution technique for determination of cardiac output in man has been studied and analyzed by several authors, and the opinions are reviewed by Dow. During hard work the technique was applied by Lee et al.,[47] Chapman et al.,[17] Astrand, et al.,[6] and Wang et al.[72] In general the method is accepted as convenient and reliable.

Calculation of the area under the recorded dye curves was done by three methods:

a) Semilogarithimic extrapolation method of Stewart - Hamilton.

b) Planimetry

c) Woods Formula

The methods were in very good agreement.-

a) The correlation coefficient between the values from Stewart Hamilton and Woods Formula is r = 0.98.

The Stewart Hamilton value = 1.02 (Woods value) - 0.01

S.D. = 0.90 n = 376

b) The correlation coefficient between the values from Stewart Hamilton and Planimetry is r = 0.98.

The Stewart Hamilton value = 1.02 (Planimetry) + 0.22

S.D. = 1.37 n = 263

c) The correlation coefficient between the values from Stewart Hamilton and Computer is r = 0.96.

The Stewart Hamilton value = 1.19 (Computer) + 0.93

S.D. = 1.50 n = 134.

Mean transit time was calculated for each dilution curve by the usual Stewart Hamilton formulas. The mean transit time was corrected for delay introduced by the sampling system. The cardio-pulmonary blood volume was calculated as a product of cardiac output and mean transit time.

All results were analysed by conventional statistical techniques for small samples. The p values have been represented by:

a) N.S. for p values greater than 0.05

b) * for p values between 0.01 and 0.05

c) * * for p values between 0.001 and 0.01

d) * * * for p values smaller than 0.001

RESULTS

Some of the anthropological data for the twelve subjects is presented in table I. Their body surface area (B.S.A.) was determined from the Dubois Body Surface Chart (prepared by Boothley and Sandiford of the Mayo Clinic).

The mean age was 24 years with an age range of 20 - 36 years. The mean weight was 76.2 kilograms (65.3 - 87.1 kilograms). The mean height was 181 centimeters (173 - 191 centimeters).

Table IIa shows the maximum oxygen uptake obtained during preliminary studies. The average values for work load, oxygen uptake and heart rate obtained during the preliminary study are listed in table IIb.

In table IIIa and IIIb individual data obtained during the preinfusion experiments is listed. The tables IVa and IVb contain the same data obtained during the postinfusion investigation.

Table V shows a comparison between the preinfusion mean resting values of this study and resting circulatory parameters of other authors. The present study agrees well with these.

Data obtained during the preinfusion maximum exercise was compared with other studies in table VI. The maximum oxygen uptakes and heart rates correspond but the maximum cardiac output in this study is somewhat low compared to the others.

The cardiovascular and respiratory values presented in the above tables pertaining to this study are all an average of the values obtained during the last two minutes of each exercise level.

HEART RATE (H.R.) AND OXYGEN CONSUMPTION (VO_2)

There was no significant difference in the heart rate and oxygen uptake obtained during the preliminary investigation and the preinfusion study (see table VIIa and VIIb).

Table VIIIa and VIIIb show similar comparisons between the pre-infusion and postinfusion values of heart rate and $\dot{V}O_2$. Again, no significant difference is noted suggesting that the infused 6% dextran solution had no effect on these parameters at rest or during exercise. The pre- and post-infusion values for heart rate and oxygen uptake are more clearly shown in figure 6 and figure 7 where each mean value with its corresponding standard deviation is plotted. A linear rise in heart rate is shown with increasing work level, confirming the findings of other authors.[14,42,45] A linear rise in $\dot{V}O_2$ with exercise occurs because it was on this criteria that the submaximal work loads were chosen.

CENTRAL BLOOD VOLUME (C.B.V.)

Central blood volume increased significantly following infusion of dextran at rest and all levels of exercise (table VIIIc). This relationship is plotted in figure 8. An increase of about 20% was noted at rest and during exercise. C.B.V. increased fairly linearly with exercise to the level of 75% of maximum oxygen uptake, but no further increase was found during maximum exercise. This suggests that maximum pulmonary vascular dilation has occured at that level.

MEAN RIGHT ATRIAL PRESSURE ($R.A.\bar{p}$)

A slight but not significant increase is noted between the pre-

infusion and postinfusion R.A.$\bar{p}$ (table VIIId). In both studies a rise in R.A.$\bar{p}$ was evident with exercise. This observation is notably different from that observed in the study with blood transfusion where a marked rise in R.A.$\bar{p}$ was observed after blood volume expansion.

CARDIAC OUTPUT (C.O.)

The average cardiac outputs with standard deviations are listed in table VIIIe. A significant increase in postinfusion over preinfusion was found at rest as well as during all levels of exercise, the increases being: 52% at rest, 35% at 25%, 28% at 50%, 23% at 75%, and 23% at maximal exertion. This increase is shown in figure 10 where the mean values with their standard deviations are plotted. Cardiac outputs at rest and during maximum exercise are similar to the values obtained by others in normal young individuals (Table V and table VI).

There is a significant increase in cardiac output with increasing work load up to 75% of the maximal $\dot{V}O_2$. From the 75% work level to the maximum, there is no significant increase in C.O. (i.e. the C.O. is reaching a plateau).

STROKE VOLUME (S.V.)

Stroke volume increased significantly following infusion of dextran at rest and at all levels of exercise. The increase was 43% at rest, 17% at 25%, 17% at 50%, 21% at 75% and 24% during maximum exertion. The significant increase in stroke volume from rest to exercise agrees with the results found by others,[2,17,51,72] and is shown in figure 9. The increase was 44% from rest to the 75% level of exercise before the infusion and 21% after the infusion. However, dur-

ing maximum exercise stroke volume decreased significantly from the 75% submaximal exercise value. This reduction was 10% preinfusion and 8% postinfusion.

ARTERIAL PRESSURE AND PERIPHERAL VASCULAR RESISTANCE (Art.$\bar{p}$ and P.V.R.)

The systolic and diastolic, as well as the mean arterial pressure before and after infusion show no significant difference (tables VIIIg, VIIIh and VIIIi). Accordingly, the calculated peripheral vascular resistance was significantly reduced following infusion (table IX).[16] The reduction in postinfusion peripheral vascular resistance was 18% during maximum exercise, over the preinfusion value. A slightly greater reduction - 21% - was obtained at the 75% exercise level.

HEMOGLOBIN (Hb.), HEMATOCRIT (Hct.) AND VISCOSITY (η).

The mean values before and after infusion were compared in tables VIIIj and VIIIk. A significant reduction was found in all of these values, which indicates there has been a significant hemodilution. The reduction during maximum exercise was 12% in Hb. and 10% in Hct.

Viscosity was measured in one subject only. A reduction of 11% was found following infusion. The decrease in viscosity agrees well with the decrease in Hb. and Hct.

BLOOD GASES AND LACTATE

No significant change was noted between the pre- and postinfusion blood gas results.

The postinfusion lactic acid levels at rest and exercise compared well with the preinfusion values. This indicates that the degree of anaerobic metabolism was similar for the two studies.

TABLE I

ANTHROPOLOGICAL DATA

SUBJECT	AGE	WEIGHT (kg.)	HEIGHT (cm.)	B.S.A.	MAX H.R.
S.L.	36	73.48	179	1.91	202
B.W.	25	77.11	183	1.97	190
R.D.	24	74.16	175	1.87	190
G.M.	21	87.09	191	2.14	180
J.L.	21	81.65	183	2.02	198
B.W.	22	81.65	182	2.01	207
W.B.	20	65.77	177	1.80	195
D.T.	20	74.84	183	1.95	200
M.G.	26	83.91	191	2.11	186
R.B.	20	81.65	180	2.00	192
B.B.	22	68.04	180	1.86	188
T.G.	33	65.32	173	1.77	180
MEAN	24	76.20	181	1.95	192

TABLE IIa

PRELIMINARY STUDIES

SUBJECT	MAX $\dot{V}_E$ *	MAX OXYGEN UPTAKE		SPORTS
		(l/min.)	(ml/kg.min.)	
S.L.	101.2	2.43	33.00	SEDENTARY
B.W.	137.8	4.01	52.02	BASKETBALL
R.D.	79.3	3.22	43.41	SEDENTARY
G.M.	110.1	4.41	50.65	BASKETBALL
J.L.	105.7	3.43	41.95	BASKETBALL
B.W.	126.6	3.51	43.00	SEDENTARY
W.B.	102.6	2.86	43.50	SEDENTARY
D.T.	108.9	3.10	41.48	SEDENTARY
M.G.	121.8	3.75	44.64	BASKETBALL
R.B.	130.9	3.74	45.81	SEDENTARY
B.B.	133.1	3.57	52.81	BASKETBALL
T.G.	107.0	3.35	51.35	RUNNING

* Determined at the time of max. $\dot{V}O_2$.

TABLE IIb

PRELIMINARY STUDIES

EXERCISE STATE	WORK LOAD (watts)	$\dot{V}O_2$ (l/min./m^2)	H.R.
REST	———	———	78 ± 14
25%	52 ± 12	.49 ± .05	99 ± 13
50%	126 ± 22	.87 ± .14	131 ± 14
75%	203 ± 36	1.31 ± .15	164 ± 15
MAX	278 ± 48	1.76 ± .19	190 ± 11

TABLE IIIa

PREINFUSION STUDIES

SUBJ.	WORK LOAD watts	$\dot{V}_E$ STPD	$\dot{V}O_2$ l/min	RQ	HR	C.O. l/min.	S.V. c.c.	C.B.V. c.c.	LACT. mg.%
1	REST	8.7	0.28	0.68	78	5.55	72	645	7.9
	30	16.9	0.57	0.83	93	7.36	79	610	12.3
	90	31.3	1.19	0.94	141	12.22	87	773	21.2
	160	59.9	2.02	1.05	186	16.00	86	941	43.1
	210	97.4	2.35	1.13	201	14.53	72	761	89.8
2	REST	10.6	0.45	0.74	70	6.30	90	666	10.4
	70	—	—	—	97	11.45	119	792	11.5
	160	48.9	2.10	0.92	135	17.00	126	929	—
	270	80.6	3.15	0.99	174	19.90	114	981	49.6
	350	122.7	3.75	1.12	189	21.25	112	1140	81.7
3	REST	6.6	0.29	0.71	80	6.16	77	644	8.7
	60	15.8	0.96	0.74	104	11.65	113	894	11.1
	120	23.8	1.33	0.83	127	14.90	120	1020	21.3
	180	39.6	2.22	0.96	161	17.60	110	1100	50.4
	240	67.9	2.85	1.16	188	19.65	105	1013	74.5

TABLE IIIa

PREINFUSION STUDIES

SUBJ.	WORK LOAD watts	$\dot{V}_E$ STPD l/min.	$\dot{V}O_2$ STPD l/min.	RQ	HR	C.O. l/min.	S.V. c.c.	C.B.V. c.c.	LACT. mg.%
4	REST	14.9	0.41	0.86	66	8.11	124	738	
	60	28.8	1.21	0.81	98	12.03	122	765	
	160	51.2	2.44	0.96	126	17.15	136	848	
	260	71.3	3.40	0.96	153	21.80	143	1205	
	360	100.7	4.33	1.11	175	22.14	127	1105	
5	REST	13.5	0.42	0.94	112	6.23	56	445	
	40	25.3	0.75	1.17	126	8.96	71	530	
	120	37.6	1.71	0.93	142	11.58	82	754	
	200	51.7	1.99	1.16	155	14.13	91	840	
	280	86.9	3.34	1.12	192	15.34	80	762	
6	REST	10.3	0.35	0.74	84	6.45	77	608	
	60	21.9	0.90	0.75	124	8.91	72	622	
	130	44.5	1.73	0.91	156	11.68	75	586	
	200	68.0	2.45	1.00	180	14.57	81	695	
	270	105.6	3.08	1.16	203	14.88	74	716	

TABLE IIIa

PREINFUSION STUDIES

SUBJ.	WORK LOAD watts	$\dot{V}_E$ STPD	$\dot{V}O_2$ l/min.	RQ	HR	C.O. l/min.	S.V. c.c.	C.B.V. c.c.	LACT. mg.%
7	REST	9.8	0.33	0.81	83	5.24	64	617	
	40	16.3	0.79	0.78	101	10.52	104	876	
	100	23.3	1.25	0.85	131	15.96	122	881	
	160	36.0	1.94	0.92	153	18.48	121	953	
	230	74.9	2.68	1.20	188	18.90	101	1038	
8	REST	9.3	0.36	0.75	100	6.34	63	690	
	60	17.1	0.68	0.80	108	9.53	89	732	
	120	39.1	1.51	0.91	140	13.02	93	847	
	180	58.0	2.25	1.00	169	16.26	96	902	
	240	97.8	2.97	1.16	194	16.38	85	890	
9	REST	7.9	0.32	0.74	80	8.65	108	844	
	40	22.7	0.95	0.77	100	13.61	139	1021	
	120	45.4	1.70	0.99	122	17.53	144	1060	
	200	67.3	2.65	0.97	157	24.62	157	1170	
	280	112.5	3.64	1.03	183	27.54	151	1205	

TABLE IIIa

PREINFUSION STUDIES

SUBJ.	WORK LOAD watts	$\dot{V}_E$ STPD	$\dot{V}O_2$ l/min.	RQ	HR	C.O. l/min.	S.V. c.c.	C.B.V. c.c.	LACT. mg.%
10	REST	9.4	0.32	0.68	72	5.47	77	745	
	60	23.0	0.88	0.77	89	10.27	117	969	
	150	44.5	1.98	0.91	125	15.92	136	1190	
	240	86.7	3.18	1.03	164	19.09	121	1350	
	330	125.6	3.73	1.07	185	18.18	99	1470	
11	REST	9.4	0.30	0.67	72	3.13	44	575	
	50	22.2	0.88	0.79	85	6.21	73	513	
	120	34.0	1.53	0.88	115	9.86	86	785	
	190	56.1	2.53	0.91	166	11.41	69	754	
	260	86.4	2.94	1.14	187	13.59	73	862	
12	REST	8.8	0.30	0.73	68	3.56	53	464	
	50	18.3	0.72	0.83	82	7.26	89	591	
	120	30.3	1.48	0.92	113	10.54	94	713	
	200	63.8	2.48	0.99	147	15.04	102	836	
	280	100.7	3.08	1.21	177	15.76	65	894	

TABLE IIIb

PREINFUSION STUDIES

SUBJ.	WORK LOAD watts	pO_2 mm. Hg.	pCO_2 mm. Hg.	pH	Hb.	Hct.	R.A. $\bar{p}$ mm. Hg.	mean mm. Hg.	Art. pr. mm. Hg.
1	REST	76	36	7.42	13.8	—	3.0	87	108/66
	30	84	33	7.42	14.0	—	2.0	94	104/66
	90	86	32	7.39	14.2	—	3.0	—	———
	160	83	27	7.34	14.4	—	5.0	111	132/80
	210	92	22	7.27	15.0	42	4.0	109	127/80
2	REST	82	38	7.41	16.6	—	1.0	97	107/79
	70	88	32	7.41	16.9	—	1.0	101	128/85
	160	89	35	7.40	17.1	—	2.0	115	140/100
	270	83	30	7.34	17.3	—	2.0	120	147/95
	350	76	29	7.34	16.7	48	4.5	141	174/113
3	REST	80	28	7.41	16.4	—	1.0	96	114/80
	60	70	39	7.38	17.7	—	1.5	98	129/82
	120	75	37	7.35	18.0	—	1.5	108	152/84
	180	80	41	7.31	18.0	—	1.5	112	163/87
	240	70	33	7.28	18.5	52	2.0	120	167/95

TABLE IIIb

PREINFUSION STIDIES

SUBJ.	WORK LOAD watts	pO_2 mm. Hg.	pCO_2 mm. Hg.	pH	Hb.	Hct.	R.A.p mm. Hg.	mean mm. Hg.	Art. pr mm. Hg.
4	REST	83	31	7.38	14.9	42	1.5	105	121/86
	60	72	29	7.37	—	—	2.0	107	129/86
	160	71	29	7.36	15.3	—	2.5	114	146/91
	260	65	29	7.34	—	—	3.0	128	164/95
	360	59	30	7.24	16.8	—	3.5	142	181/112
5	REST	70	37	7.44	16.0	48	-3.0	—	—
	40	72	35	7.45	16.5	46	-0.5	101	129/83
	120	74	36	7.40	16.3	46	0.5	104	133/87
	200	71	35	7.35	16.6	45	2.0	118	152/95
	280	65	34	7.25	17.3	49	9.0	124	169/95
6	REST	73	40	7.35	14.9	42	1.0	102	114/85
	60	75	41	7.33	14.7	43	0.5	108	130/80
	130	73	39	7.34	15.3	43	0.5	115	142/90
	200	72	37	7.28	16.6	43	2.0	123	148/98
	270	72	35	7.26	17.3	48	5.5	128	156/104

TABLE IIIb

PREINFUSION STUDIES

SUBJ.	WORK LOAD watts	pO_2 mm. Hg.	pCO_2 mm. Hg.	pH	Hb.	Hct.	R.A.p mean mm. Hg.		Art. pr mm. Hg.
7	REST	88	42	7.33	16.5	45	4.0	82	91/68
	40	80	42	7.36	16.1	43	2.0	85	106/64
	100	64	40	7.40	15.1	41	2.0	85	110/64
	160	65	42	7.32	15.3	41	2.0	97	121/70
	230	77	41	7.27	15.6	46	3.0	95	125/70
8	REST	66	42	7.32	14.9	46	-3.0	91	121/64
	60	66	42	7.29	15.2	37	3.0	92	126/64
	120	69	39	7.28	15.5	44	2.0	91	129/68
	180	66	40	7.24	15.5	44	4.0	93	133/70
	240	62	39	7.23	15.5	43	7.5	95	140/72
9	REST	79	29	7.41	13.8	40	3.0	89	106/72
	40	87	30	7.40	13.7	38	5.0	85	112/72
	120	87	32	7.44	13.8	38	6.5	90	114/76
	200	65	30	7.34	13.4	38	5.0	95	116/83
	280	78	24	7.23	14.8	40	—	110	144/87

TABLE IIIb

PREINFUSION STUDIES

SUBJ.	WORK LOAD watts	pO_2 mm. Hg.	pCO_2 mm. Hg.	pH	Hb.	Hct.	R.A.$\bar{p}$ mm. Hg.	mean mm. Hg.	Art. pr mm. Hg.
10	REST	69	33	7.38	14.5	44	0.5	102	123/83
	60				14.8	44	3.0	118	142/92
	150	69	33	7.32	14.5	41	5.0	129	165/103
	240	61	30	7.23	14.9	42	6.5	139	184/109
	330	58	28	7.20	15.1	43	4.0	146	191/116
11	REST	73	34	7.44	15.5	41	1.0	90	101/72
	50	75	35	7.43	16.6	47	2.0	96	120/75
	120	76	38	7.41	16.7	48	1.5	109	134/85
	190	86	35	7.39	16.9	47	1.5	124	154/97
	260	74	32	7.38	17.5	48	6.0	131	170/97
12	REST	67	35	7.38	15.0	42	5.0	99	123/90
	50	64	38	7.37	15.2	42	5.5	107	142/85
	120	71	39	7.36	15.6	42	4.0	118	151/92
	200	69	32	7.36	16.2	44	6.0	128	170/99
	280	70	30	7.25	17.0	46	6.5	132	175/101

TABLE IVa

POSTINFUSION STUDIES

SUBJ.	WORK LOAD watts	$\dot{V}_E$ STPD	$\dot{V}O_2$ l/min.	RQ	HR	C.O. l/min.	S.V. c.c.	C.B.V. c.c.	LACT. mg.%
1	REST	7.6	0.23	0.68	90	6.96	77	642	7.9
	30	16.5	0.60	0.79	110	7.74	70	511	12.4
	90	31.7	1.12	1.00	138	12.15	88	990	25.7
	160	67.7	1.94	1.14	177	17.98	102	1012	46.9
	210	92.1	2.24	1.19	195	18.49	95	1110	89.9
2	REST	10.4	0.41	0.77	77	9.30	121	790	11.0
	70	26.2	1.17	0.81	111	14.60	131	824	12.9
	160	55.3	2.14	1.00	148	22.00	149	1230	24.9
	270	89.7	3.25	1.01	175	23.60	135	1050	54.4
	350	126.0	3.81	1.12	190	26.30	139	1350	72.4
3	REST	9.9	0.48	0.72	86	11.48	134	995	9.3
	60	22.2	1.08	0.82	124	15.90	129	1003	11.9
	120	32.7	1.66	1.00	150	19.50	130	1000	21.7
	180	48.1	2.32	1.00	163	19.75	121	1210	53.9
	240	72.3	2.99	1.11	184	24.75	135	1255	73.4

TABLE IVa

POSTINFUSION STUDIES

SUBJ.	WORK LOAD watts	$\dot{V}_E$ STPD	$\dot{V}O_2$ l/min.	RQ	HR	C.O. l/min.	S.V. c.c.	C.B.V. c.c.	LACT. mg. %
4	REST	13.9	0.45	0.82	72	8.29	116	811	
	60	35.2	1.23	0.90	105	14.70	140	858	
	160	50.4	2.11	—	129	19.70	152	1064	
	260	75.6	3.18	1.03	150	30.55	204	1705	
	360	107.9	4.10	1.17	174	27.65	160	1365	
5	REST	14.4	0.49	0.97	111	9.18	83	620	
	40	26.3	0.91	1.09	136	11.26	84	706	
	120	39.8	1.61	1.05	144	14.07	98	682	
	200	57.8	2.44	1.06	166	16.13	97	767	
	280	87.9	3.12	1.21	188	15.77	90	869	
6	REST	8.2	0.26	0.75	97	8.81	91	706	
	60	24.8	1.07	0.70	123	12.30	100	748	
	130	42.1	1.85	0.75	162	15.93	98	810	
	200	73.7	2.72	0.97	184	18.18	99	880	
	270	122.5	3.48	1.04	191	16.81	88	973	

TABLE IVa

POSTINFUSION STUDIES

SUBJ.	WORK LOAD watts	$\dot{V}_E$ STPD l/min.	$\dot{V}O_2$ STPD l/min.	RQ	HR	C.O. l/min.	S.V. c.c.	C.B.V. c.c.	LACT. mg. %
7	REST	10.4	0.44	0.74	88	12.19	139	1030	
	40	14.6	0.92	0.68	118	17.11	145	1130	
	100	26.9	1.36	0.83	138	19.65	142	1122	
	160	39.4	2.09	0.95	158	23.56	150	1555	
	230	84.8	2.75	1.19	194	23.03	119	1160	
8	REST	10.9	0.41	0.64	89	8.44	95	747	
	60	19.5	0.88	0.71	114	12.89	113	921	
	120	40.3	1.62	0.91	148	15.78	107	974	
	180	62.9	2.25	1.03	174	21.81	125	1230	
	240	101.5	2.86	1.16	195	19.78	101	955	
9	REST	10.2	0.42	0.78	84	10.87	129	919	
	40	19.3	0.77	0.79	115	16.21	141	1090	
	120	48.1	1.77	0.91	139	23.23	167	1230	
	200	87.5	2.80	1.05	153	25.36	166	1420	
	280	117.6	3.62	1.10	185	25.12	136	1230	

TABLE IVa

POSTINFUSION STUDIES

SUBJ.	WORK LOAD watts	$\dot{V}_E$ STPD 1/min.	$\dot{V}O_2$ STPD 1/min.	RQ	HR	C.O. 1/min.	S.V. c.c.	C.B.V. c.c.	LACT. mg.%
10	REST	10.1	0.40	0.71	77	8.51	111	884	
	60	24.3	0.98	0.76	108	14.61	135	1060	
	150	51.2	1.87	0.97	147	21.78	148	1220	
	240	87.2	3.08	1.03	176	21.48	122	1355	
	330	127.7	3.50	1.12	190	25.09	132	1615	
11	REST	13.7	0.37	0.85	77	8.69	114	881	
	50	—	—	—	108	11.85	110	953	
	120	38.9	1.70	0.88	132	16.54	126	1094	
	190	56.4	2.30	0.95	158	20.06	127	1195	
	260	114.5	3.25	1.16	183	19.65	108	1265	
12	REST	7.8	0.29	0.70	65	4.75	73	529	
	50	15.6	0.70	0.76	100	9.62	96	748	
	120	30.6	1.53	0.83	129	14.43	112	911	
	200	62.4	2.56	0.95	153	17.94	118	968	
	280	100.4	3.32	1.11	177	20.36	115	1204	

TABLE IVb

POSTINFUSION STUDIES

SUBJ.	WORK LOAD watts	pO_2 mm. Hg.	pCO_2 mm. Hg.	pH	Hb.	Hct.	R.A. $\bar{p}$ mm. Hg.	mean mm. Hg.	Art. pr. mm. Hg.
1	REST	76	35	7.42	12.1	—	-3.0	76	100/71
	30	82	36	7.44	12.3	—	-0.5	83	100/66
	90	87	33	7.41	12.1	—	0.0	94	113/71
	160	78	28	7.38	12.6	—	3.0	106	127/80
	210	78	26	7.31	12.3	36	5.0	111	142/80
2	REST	83	37	7.41	13.3	—	1.0	95	107/66
	70	78	38	7.41	13.9	—	1.0	102	121/73
	160	83	35	7.41	14.5	—	1.0	111	149/88
	270	76	28	7.36	11.6	—	1.5	118	154/96
	350	82	32	7.36	14.9	46	2.5	136	170/108
3	REST	69	37	7.40	13.7	40	4.0	86	114/76
	60	70	38	7.35	14.1	40	6.0	96	129/82
	120	65	39	7.37	14.4	40	5.0	106	144/84
	180	82	37	7.33	14.9	42	5.5	111	155/89
	240	68	33	7.38	15.4	42	6.0	122	167/96

TABLE IVb

POSTINFUSION STUDIES

SUBJ.	WORK LOAD watts	pO_2 mm. Hg.	pCO_2 mm. Hg.	pH	Hb.	Hct.	R.A.$\bar{p}$ mm. Hg.	mean mm. Hg.	Art.pr. mm. Hg.
4	REST	81	28	7.49	13.5	41	3.0	99	114/82
	60	78	30	7.47	13.2	40	4.0	112	131/90
	160	76	29	7.43	13.6	37	3.0	117	142/91
	260	71	29	7.34	14.2	37	4.0	123	159/95
	360	69	30	7.34	14.8	39	5.0	148	181/112
5	REST	76	35	7.42	13.6	41	1.0	96	118/80
	40	75	32	7.42	14.3	42	1.5	106	125/91
	120	70	33	7.40	—	—	4.5	110	138/95
	200	72	33	7.34	14.3	40	7.5	116	142/99
	280	64	33	7.28	15.9	45	11.0	126	164/102
6	REST	70	36	7.36	13.3	32	4.0	103	117/85
	60	66	34	7.37	12.9	35	2.0	107	128/85
	130	66	35	7.32	13.5	35	3.0	113	138/88
	200	73	34	7.27	14.3	37	3.0	121	148/96
	270	68	30	7.20	14.9	38	7.0	127	154/102

TABLE IVb

POSTINFUSION STUDIES

SUBJ.	WORK LOAD watts	pO_2 mm. Hg.	pCO_2 mm. Hg.	pH	Hb.	Hct	R.A.p mean mm. Hg.		Art. pr. mm. Hg.
7	REST	92	39	7.38	12.5	35	-1.0	80	91/66
	40	74	42	7.38	12.1	34	2.0	89	102/64
	100	79	44	7.32	13.1	35	2.0	91	110/72
	160	69	46	7.26	13.6	35	4.0	100	121/72
	230	81	36	7.20	14.3	35	5.0	104	125/83
8	REST	69	29	7.42	13.0	38	2.0	93	121/72
	60	62	36	7.34	13.0	32	1.0	95	129/72
	120	65	36	7.33	13.8	35	0.0	96	136/76
	180	73	33	7.29	14.1	36	3.5	97	144/80
	240	69	28	7.28	14.4	40	12.0	104	152/80
9	REST	68	32	7.43	11.3	30	—	80	102/68
	40	57	33	7.39	11.4	29	—	87	106/74
	120	57	31	7.45	11.3	28	—	95	119/76
	200	69	29	7.39	11.7	33	—	102	129/85
	280	69	27	7.28	12.3	34	—	114	144/92

TABLE IVb

POSTINFUSION STUDIES

SUBJ.	WORK LOAD watts	pO_2	pCO_2	pH	Hb.	Hct.	R.A.p	mean	Art. pr.
		mm. Hg.					mm. Hg.		
10	REST	—	—	—	13.1	39	0.5	98	120/81
	60	66	32	7.45	13.2	38	0.5	120	141/94
	150	60	31	7.43	13.6	36	3.0	130	163/99
	240	60	27	7.34	14.1	39	6.5	142	189/113
	330	89	25	7.21	14.0	40	7.0	142	189/118
11	REST	63	46	7.40	13.5	37	4.5	98	114/79
	50	70	44	7.34	13.9	38	6.0	101	118/81
	120	71	48	7.32	14.2	34	5.0	109	134/91
	190	70	46	7.30	14.6	37	4.5	116	148/85
	260	60	39	7.29	15.5	40	8.0	126	166/91
12	REST	74	33	7.40	12.2	32	3.0	92	113/85
	50	76	40	7.39	12.7	36	5.5	104	132/85
	120	68	36	7.36	13.1	36	—	—	——
	200	73	29	7.35	13.9	39	—	119	156/94
	280	73	26	7.26	15.0	40	—	128	170/94

TABLE V

RESEARCH GROUP	AGE of SUBJECTS	$\dot{V}O_2$ (mls)	C.O. (l/min.)	H.R. (Beats /min.)	S.V. (mls)	A - V DIFF. (mls/l)	HT. (cms)	WT. (kgm)
Robinson et al. n = 5 Bicycle	26 (19 - 36)	--	5.34 ± 1.41	84 ± 22	65 ± 14	--	--	--
Mitchell et al. Treadmill	-- (20 - 29)	340 ± 40 n = 5	540 ± 0.80 n = 14	91 ± 17 n = 14	62 ± 18 n = 13	65 ± 07 n = 5	--	--
Saltin et al. Bicycle	--	336	5.7	61	96	59.6	--	69.2
This study n = 12 Biccyle	24 (20 - 36)	350 ± 39	5.9 ± 1.6	80 ± 14	75 ± 23	59	181	76.2

TABLE VI

RESEARCH GROUP	AGE of SUBJECTS	$\dot{V}O_2$ (mls)	C.O. (l/min.)	H.R. (Beats /min.)	S.V. (mls)	A - V DIFF. (mls/l)	WT. (cms)	HT. (kgm)
Robinson et al. n = 5	26 (19 - 36)	3200	21.6	176	123	148	--	--
Mitchell et al. n = 23	-- (20 - 29)	3200	23.4	187	125	134	--	--
Astrand et al. n = 8	23 (19 - 27)	3100	22.8	198	115	136	179	70
This study n = 12 Preinfusion	24 (20 - 36)	3200	18.2	189	108	176	181	76

TABLE VIIa

HEART RATE (Beats per minute)

	REST	25%	50%	75%	MAX
PRELIM	78 ± 14	98 ± 13	131 ± 14	164 ± 15	190 ± 11
PRE	80 ± 14	101 ± 14	131 ± 12	164 ± 12	189 ± 8
p	N.S.	N.S.	N.S.	N.S.	N.S.

TABLE VIIb

OXYGEN UPTAKE (Liters per minute)

PRELIM	0.39 ± 0.07	0.97 ± 0.14	1.71 ± 0.31	2.57 ± 0.38	3.43 ± 0.46
PRE	0.38 ± 0.08	0.91 ± 0.18	1.70 ± 0.29	2.57 ± 0.43	3.25 ± 0.50
p	N.S.	N.S.	N.S.	N.S.	N.S.

TABLE VIIIa

HEART RATE (Beats per minute)

	REST	25%	50%	75%	MAX
PRE	80 ± 14	101 ± 14	131 ± 12	164 ± 11	189 ± 8
POST	84 ± 12	114 ± 10	142 ± 10	164 ± 11	187 ± 7
p	N.S.	*	*	N.S.	N.S.

TABLE VIIIb

OXYGEN UPTAKE (Liters per minute)

PRE	0.35 ± 0.05	0.84 ± 0.16	1.66 ± 0.30	2.52 ± 0.49	3.22 ± 0.55
POST	0.38 ± 0.08	0.91 ± 0.18	1.70 ± 0.29	2.57 ± 0.43	3.25 ± 0.50
p	N.S.	N.S.	N.S.	N.S.	N.S.

TABLE VIIIc

CENTRAL BLOOD VOLUME (Milliliters)

PRE	640 ± 110	740 ± 170	870 ± 170	980 ± 200	990 ± 220
POST	800 ± 150	880 ± 180	1100 ± 360	1200 ± 280	1200 ± 200
p	* *	* *	* *	* *	* *

TABLE VIIId

MEAN RIGHT ATRIAL PRESSURE - R.A.$\bar{p}$. (Mm. of Mercury)

	REST	25%	50%	75%	MAX
PRE	1.1 ± 2.4	2.0 ± 1.7	2.2 ± 1.2	3.0 ± 1.7	4.9 ± 2.1
POST	1.7 ± 2.7	2.8 ± 2.3	2.9 ± 1.7	4.2 ± 1.9	6.2 ± 2.5
p	N.S.	N.S.	N.S.	N.S.	N.S.

TABLE VIIIe

CARDIAC OUTPUT (Liters per minute)

PRE	5.9 ± 1.6	9.8 ± 2.2	14.0 ± 2.8	17.4 ± 3.7	18.2 ± 4.0
POST	9.0 ± 2.0	13.2 ± 2.8	17.9 ± 3.6	21.4 ± 4.0	22.3 ± 4.0
p	* *	* *	* *	* *	* *

TABLE VIIIf

STROKE VOLUME (Milliliters)

PRE	75 ± 23	99 ± 23	108 ± 25	108 ± 26	97 ± 24
POST	107 ± 23	116 ± 25	126 ± 26	130 ± 31	120 ± 23
p	* *	* *	* *	* *	* *

TABLE VIIIg

SYSTOLIC PRESSURE (Mm. of Mercury)

	REST	25%	50%	75%	MAX
PRE	112 ± 10	125 ± 11	138 ± 16	149 ± 20	160 ± 21
POST	111 ± 9	121 ± 13	135 ± 16	148 ± 18	160 ± 18
p	N.S.	N.S.	N.S.	N.S.	N.S.

TABLE VIIIh

DIASTOLIC PRESSURE (Mm. of Mercury)

PRE	77 ± 9	79 ± 10	85 ± 12	90 ± 12	95 ± 15
POST	76 ± 7	80 ± 10	85 ± 10	90 ± 11	97 ± 12
p	N.S.	N.S.	N.S.	N.S.	N.S.

TABLE VIIIi

MEAN AORTIC PRESSURE (Mn. of Mercury)

PRE	95 ± 7	99 ± 10	107 ± 13	116 ± 15	123 ± 17
POST	91 ± 9	100 ± 11	107 ± 12	114 ± 12	124 ± 13
p	N.S.	N.S.	N.S.	N.S.	N.S.

TABLE VIIIj

HEMOGLOBIN (Grams per 100 mls. of blood)

	REST	25%	50%	75%	MAX
PRE	15.2 ± 1.0	15.6 ± 1.3	15.6 ± 1.2	15.9 ± 1.4	16.4 ± 1.2
POST	12.9 ± 0.7	13.1 ± 0.9	13.4 ± 1.0	13.7 ± 1.1	14.5 ± 1.1
p	* *	* *	* *	* *	* *

TABLE VIIIk

HEMATOCRIT (Percent)

PRE	43.5 ± 2.7	42.5 ± 3.5	42.8 ± 3.4	43.0 ± 2.7	45.4 ± 3.1
POST	37.8 ± 6.1	37.3 ± 4.3	36.3 ± 5.1	38.8 ± 3.2	40.8 ± 3.9
p	* *	* *	* *	* *	* *

TABLE VIIIl

TOTAL PERIPHERIAL RESISTANCE (Peripherial resistance units)*

PRE	0.96	0.59	0.45	0.39	0.39
POST	0.60	0.44	0.35	0.31	0.32
p	* *	* *	* *	* *	* *

* Calculated from: $\frac{\text{Art. } \bar{p}. - \text{R.A.} \bar{p}.}{\text{C.O. in mls/sec.}}$

DISCUSSION

This study has shown that cardiac output (stroke volume) increases significantly following dextran infusion at all levels of exercise including the maximum. Since there was no change in heart rate at the 75% and maximal working levels, the increase in cardiac output noted in the postinfusion study must be attributed to changes in stroke volume. Of the three parameters controlling stroke volume, the latter two (the afterload and the end-diastolic volume) probably contribute most at maximal exertion. The third parameter, myocardial contraction, was assumed to be relatively constant for both studies as the heart should have been in a maximum inotropic state during maximum exercise.

The volume change due to dextran may have increased stroke volume by augmenting end-diastolic volume. However, as previous studies have shown, an increase in blood volume (and hence an increase in venous return) alone will not result in an increase in maximal cardiac output. Therefore, the increase in stroke volume after the infusion of dextran must have been due to a decreased afterload.[29]

A decrease in aortic impedence (which depends mainly upon the peripheral resistance) can be shown from Poiseuille's Law. It states that the resistance depends upon the parallel and series sum of the radius of the resistance vessels, the viscosity* and the length of the vasculature.

$$R = \frac{\Delta P}{F} = \frac{8\eta l}{\pi r^4}$$

R = resistance to blood flow
ΔP = mean pressure difference in mm. Hg.
F = flow in c.c./second.
l = length of vessels in cms.
r = mean radius of the blood vessels in cms.

η = viscosity in centipoises

There was a significant change in the viscosity following dextran infusion (for one subject it was calculated to be 11%). The change was due to the reduction in Hb. and Hct. which have been previously shown to be directly related to viscosity.[42] However, the increase in stroke volume, 24% during maximum exercise, was above that which could be expected from changes in viscosity alone. This indicates (from Poiseuille's Law) that peripheral vasodilation of resistance vessels has occured following dextran infusion. Guyton has shown this effect in dogs at rest.[42] Although no experimental evidence has shown this to be true with exercise, it seems fair to assume the relative vasodilation at rest should exist throughout the exercising state. Thus, a combination of reduced viscosity and increased radius accounts for the decreased afterload on

*Viscosity was measured by an Oswald Viscometer. Six determinations of each blood sample were measured in two different viscometers. The relative viscosity (the preinfusion viscosity divided by the postinfusion viscosity) was calculated from the formula:

$$\eta_{rel} = \frac{c\rho t}{c\rho_o t_o}$$

c = a constant depending on the dimensions of the capillary
ρ = density of preinfusion blood
ρ_o = density of postinfusion blood
t = time for preinfusion blood
t_o = time for postinfusion blood

If the viscosities of the two samples of blood are measured in the same viscometer, the relative viscosity is independent of the dimensions of the capillary as given by c. The density of the preinfusion and postinfusion exercise blood were, respectively, 1.085 gm/cc. and 1.070 gm/cc. The average time values were 297.6 and 271.2 seconds respectively. Therefore:

$$\eta_{rel} = \frac{(1.085)(297.6)}{(1.070)(271.2)} = 1.11$$

This shows an 11% decrease in blood viscosity in the postinfusion state.

the left ventricle. In the postinfusion state this results in an increase in flow over that found in the preinfusion study.

The second part of this thesis was concerned with the changes in cardiac output and stroke volume as a function of the different intensities of exercise. Cardiac output was found to almost reach a maximum value at the 75% level of maximal exertion (maximum $\dot{V}O_2$). This provides further evidence that the limiting factor of maximum $\dot{V}O_2$ (a maximum level of exercise) is the oxygen transport capacity of the circulatory system (i.e. cardiac output).

Only Saltin[59] and his colleagues have studied the circulation during submaximum as well as maximum exercise. However, they did not attempt to investigate specific levels of submaximum exercise such as the 25%, 50%, 75% levels as was done in this study. In their study, the stroke volume was found to reach a maximum level with moderate exercise and showed no reduction during the maximal exertion.

The decrease in stroke volume found in this study with increasing intensities of exercise was probably due to a reduction in end-diastolic volume. The other two parameters controlling stroke volume (myocardial contraction and afterload) would increase in intensity with exercise, tending to augment the amount of blood ejected per beat. However, this increase was off set by a greater decrease in end-dialstolic volume. Kjellberg[46] has noted a decrease in heart size with heart rates above 140 beats per minute.

Since end-diastolic volume is dependent upon three variables, all three must be examined to determine the decrease in stroke volume.

The first parameter, an increase in blood volume, has been shown to increase stroke volume at rest and submaximal levels of exercise,[47,55] but not at maximal exertion. The second factor, diastolic filling time, is shown to decrease almost linearly in the maximal region with increased heart rate (figure 15). It must be this decreased filling time that results in a decreased end-diastolic volume, and hence a fall in stroke volume at maximum. This appears to be so even with an increase in ventricular filling pressure (third factor).

Stroke volume was found in both pre- and post-infusion studies to be a parabolic function of heart rate, right atrial pressure and arterial pressure. For the preinfusion study:

$$S.V. = -6.1(R.A.\bar{p})^2 + 39\,(R.A.\bar{p}) + 45.5$$

$$400S.V. = -2.95(H.R.)^2 + 838(H.R.) - 15484$$

$$100S.V. = -10.8(Art.\bar{p})^2 + 2398(Art.\bar{p}) - 121967$$

For the postinfusion studies:

$$S.V. = -3.3(R.A.\bar{p})^2 + 39\,(R.A.\bar{p}) + 69$$

$$400S.V. = -4.0(H.R.)^2 + 1248(H.R.) - 45344$$

$$25S.V. = -2.0(Art.\bar{p})^2 + 444(Art.\bar{p}) - 21392$$

Since stroke volume is a parabolic function it has a maximal value corresponding with an optimum value for each of the functions. For the preinfusion studies, optimum

$S.V. = 111$ c.c.

$H.R. = 142$ beats/minute

$R.A.\bar{p} = 3.5$ mm. Hg.

$Art.\bar{p} = 111$ mm. Hg.

The observed maximum stroke volume at the optimum heart rate of 142 agrees well with the obervation of Kjellberg[46] that "heart size appears to diminish with levels of exercise which elevate the heart rate beyond 140 to 160 beats/minute." In this case the heart rate above 142 beats/minute correspond to a decrease in stroke volume.

The optimum values for the postinfusion studies are:

S.V. = 130 c.c.

H.R. = 156 beats/minute

R.A.$\bar{p}$ = 4.3 mm. Hg.

Art.$\bar{p}$ = 111 mm. Hg.

The postinfusion values did not fit the parabolic equation as readily as the preinfusion values, although optimum values were obtained in each case. Looking at these values we see that the optimum H.R., and R.A.$\bar{p}$ have increased after dextran infusion whereas the optimum Art.$\bar{p}$ remains the same. This, along with the fact that R.A.$\bar{p}$ did not rise with exercise as it did in the blood transfusion exercise study, indicates that the right ventricle was able to remove the venous return blood almost as rapidly as it was returned to the right atrium. If the viscosity of the blood is lowered, as with the dextran infusion, the heart is able to increase its pumping capacity by increasing the S.V. The diastolic filling time was much reduced at maximal work corresponding to an average filling time of 0.15 seconds - see figure 15.

The importance of the optimum right atrial pressure was emphasized by Guyton in dog studies.[42] It would appear that a further rise in R.A.$\bar{p}$ above the optimum level would reduce the stroke volume by

reducing venous return to the right atrium. Similarily, further increase in heart rate above the optimum level tends to reduce stroke volume by reducing the diastolic filling period, see figure 15. The rise in right atrial pressure observed between the 75% and maximal working levels was not enough to compensate for the reduction in filling time, thus, a reduction in stroke volume at maximal exertion.

The initial rise in stroke volume is mostly due to the increased contraction of the atria - augmenting ventricular filling - and increased inotropism.

The relationship between the oxygen uptake and cardiac output during supine submaximal exercise was carefully analyzed by Holmgren and Ekelund.[27] They found that C.O. is a linear function of $\dot{V}O_2$ during submaximal exercise ($C.O. = 5.8\dot{V}O_2 + 7.03$). When the resting values were included the equation was: ($C.O. = 6.3\dot{V}O_2 + 6.17$).

However, a valid comparison could not be made with this study as their results were obtained during supine exercise and maximum or near maximum exercise was not carried out.

The cardiac output versus oxygen uptake relationship for the perinfusion portion of this study - figure 11 - follows a linear relationship in the submaximal region (to the 75% work level) and plateaus at the maximal working level. The linear regression equation for this submaximal region is:

$$C.O. = 3.51\dot{V}O_2 + 8.14 \quad (n = 35 \quad S.D. = 3.2 \quad r = 0.76)$$

The equation for all preinfusion values (shown in figure 11) is:

$$C.O. = 4.02\dot{V}O_2 + 6.33 \quad (n = 59 \quad S.D. = 2.7 \quad r = 0.86)$$

Evaluating the postinfusion results in a similar way (figure 12) a linear relationship is again seen in the submaximal region of C.O. versus $\dot{V}O_2$. A plateau is evident at the maximal mean value. The overall regression equation is:

$$C.O. = 4.7\dot{V}O_2 + 8.39 \quad (n = 59 \quad S.D. = 3.0 \quad r = 0.87)$$

Comparing figures 11 and 12 it becomes apparent that C.O. starts at a much higher level per $\dot{V}O_2$ value and increases more rapidly per $\dot{V}O_2$ in subjects with dextran induced anemia and lowered viscosity.

From Fick's equation we can further examine the circulatory perameters of oxygen transport by inspecting the A-V Difference versus $\dot{V}O_2$ relationship. Fick's equation: $\dot{V}O_2 = C.O. \times$ A-V Difference. Since it has been extablished that the relationship between C.O. and $\dot{V}O_2$ can be described as linear in nonathletes during submaximal exercise in the sitting position, then the relationship between A-V Difference and $\dot{V}O_2$ should be a hyperbola. This was found by Ekelund and Holmgren[27] to be true. However, from the experimental data (both preinfusion and postinfusion) in this study, the relationship appears to be more linear - see figure 13 and 14 - then hyperbolic. The deviation is not significant and the discrepancy may be due to the fact that the C.O. versus $\dot{V}O_2$ relationship is not perfectly linear. For both preinfusion and postinfusion the theoretical A-V Difference - $\dot{V}O_2$ relationship and the mean experimental values fall within the standard deviation of the regression line.

Two components of the Fick equation which are directly related

to the cardiac output are the heart rate and stroke volume. Table VIIIc gives the pre- and post-infusion mean values. Note that there is no significant difference between the heart rate values of the two studies in the resting state and in the 75% and maximal levels of exercise. There is a significant difference in H.R. of the 25% and 50% work levels. This significant rise in heart rate during the postinfusion study corresponds to a percentage decrease in stroke volume - figure 9. The postinfusion resting S.V. increases 43% over the preinfusion exercise values. The significant rise in postinfusion H.R. corresponds to the two low increases in S.V. (the 17% values).

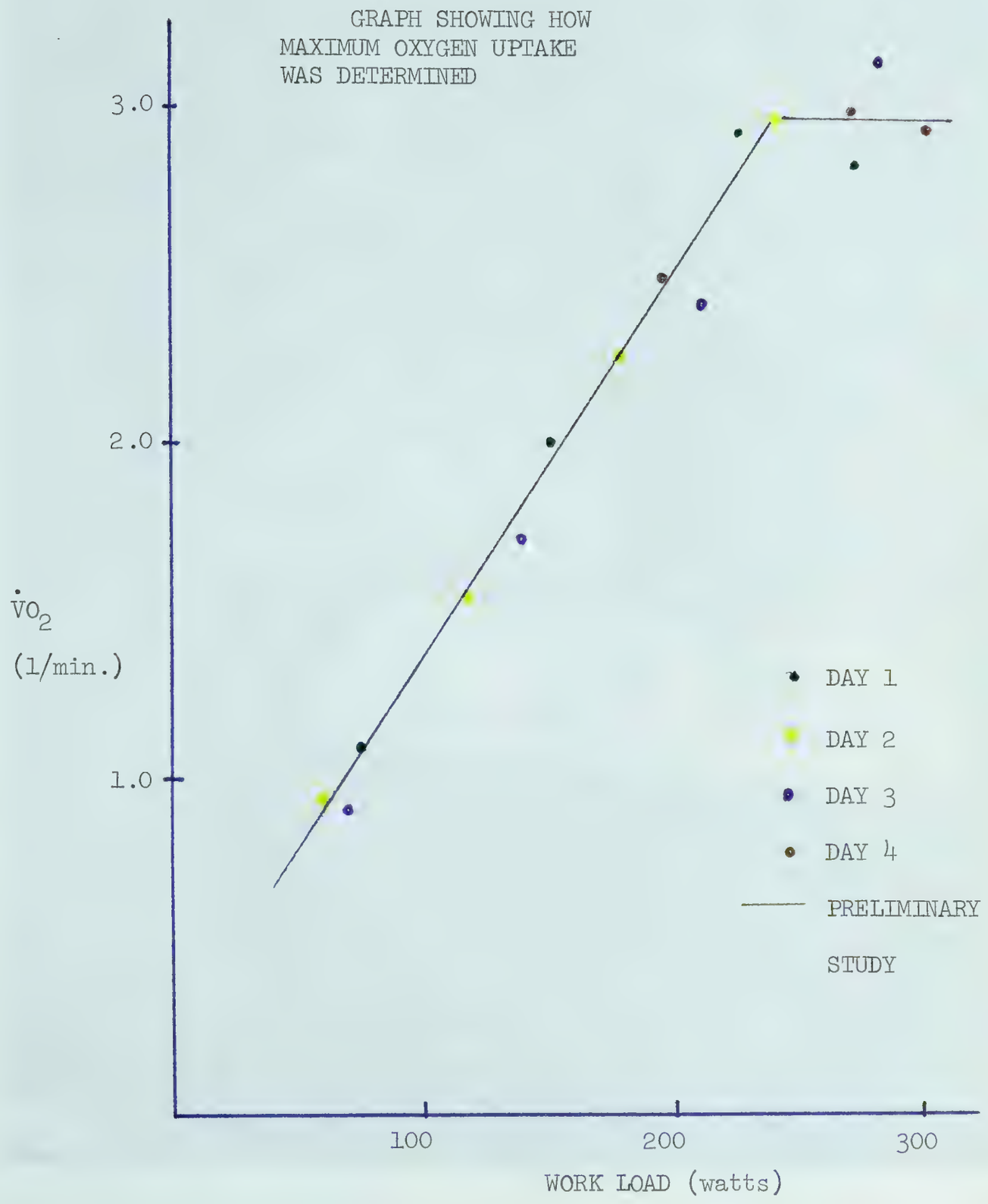

GRAPH SHOWING HOW
MAXIMUM OXYGEN UPTAKE
WAS DETERMINED
3.0
2.0
1.0
$\dot{V}O_2$
(l/min.)
100
200
300
WORK LOAD (watts)
DAY 1
DAY 2
DAY 3
DAY 4
PRELIMINARY
STUDY

Figure 1

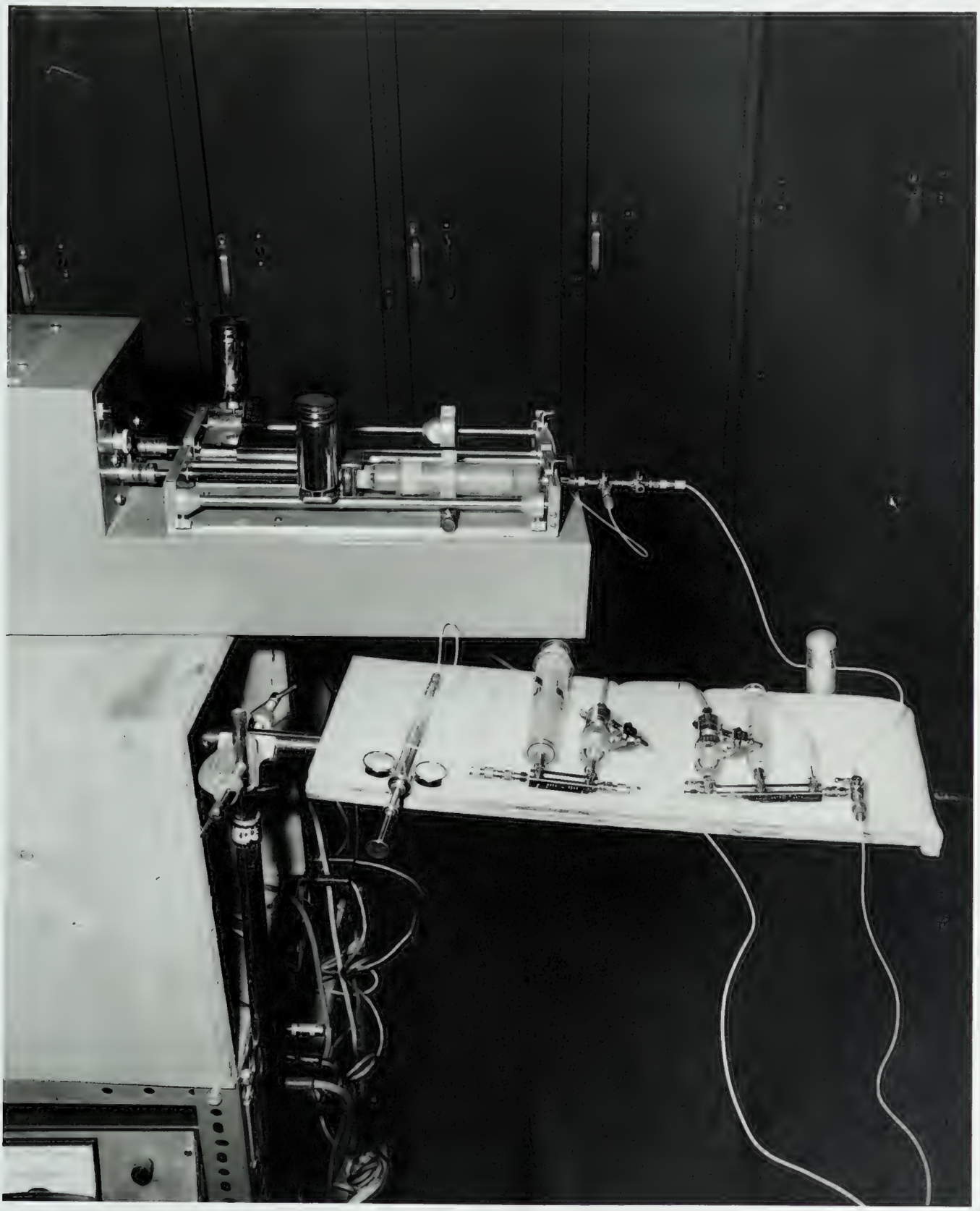


Figure 2

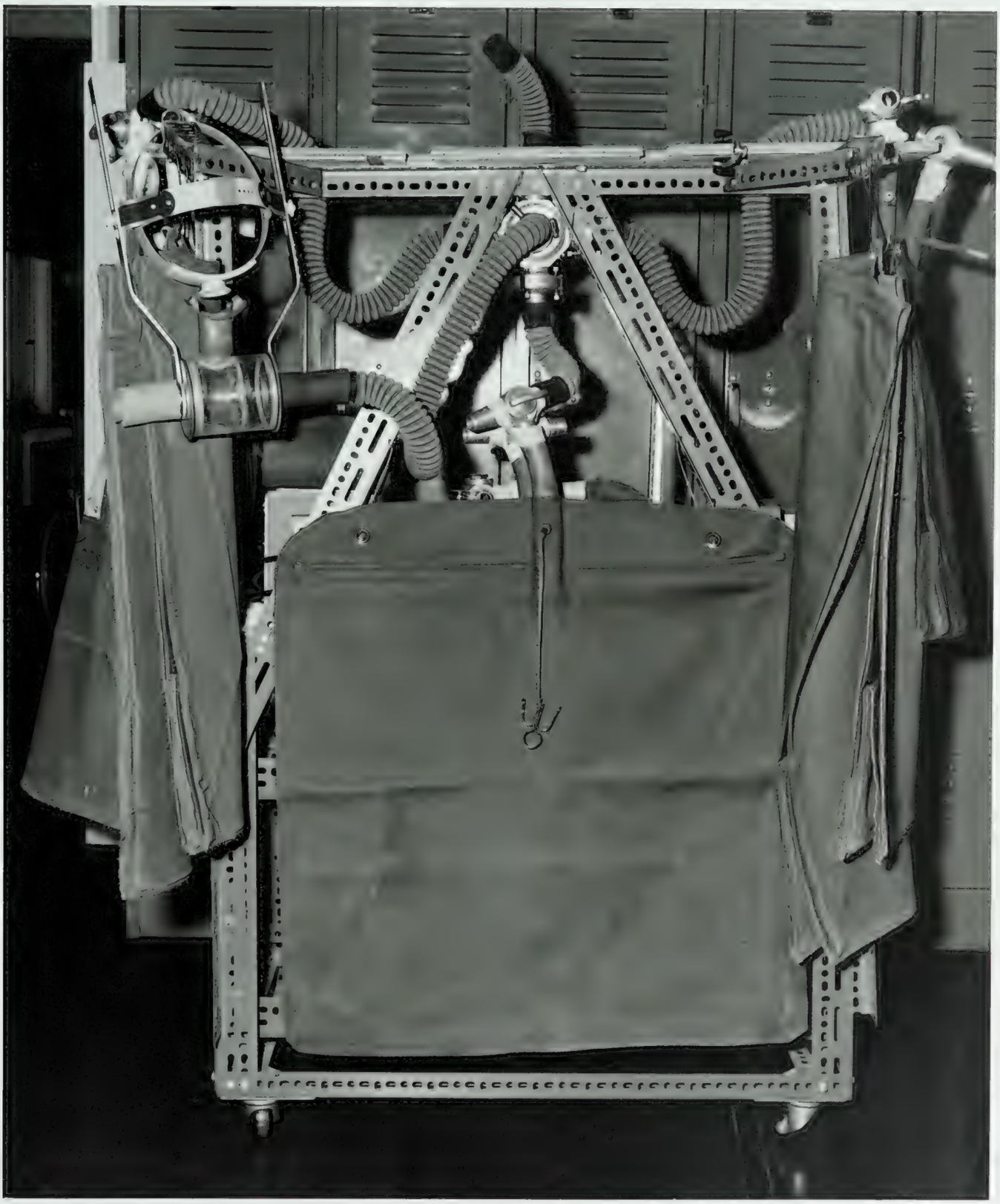


Figure 3

Figure 4

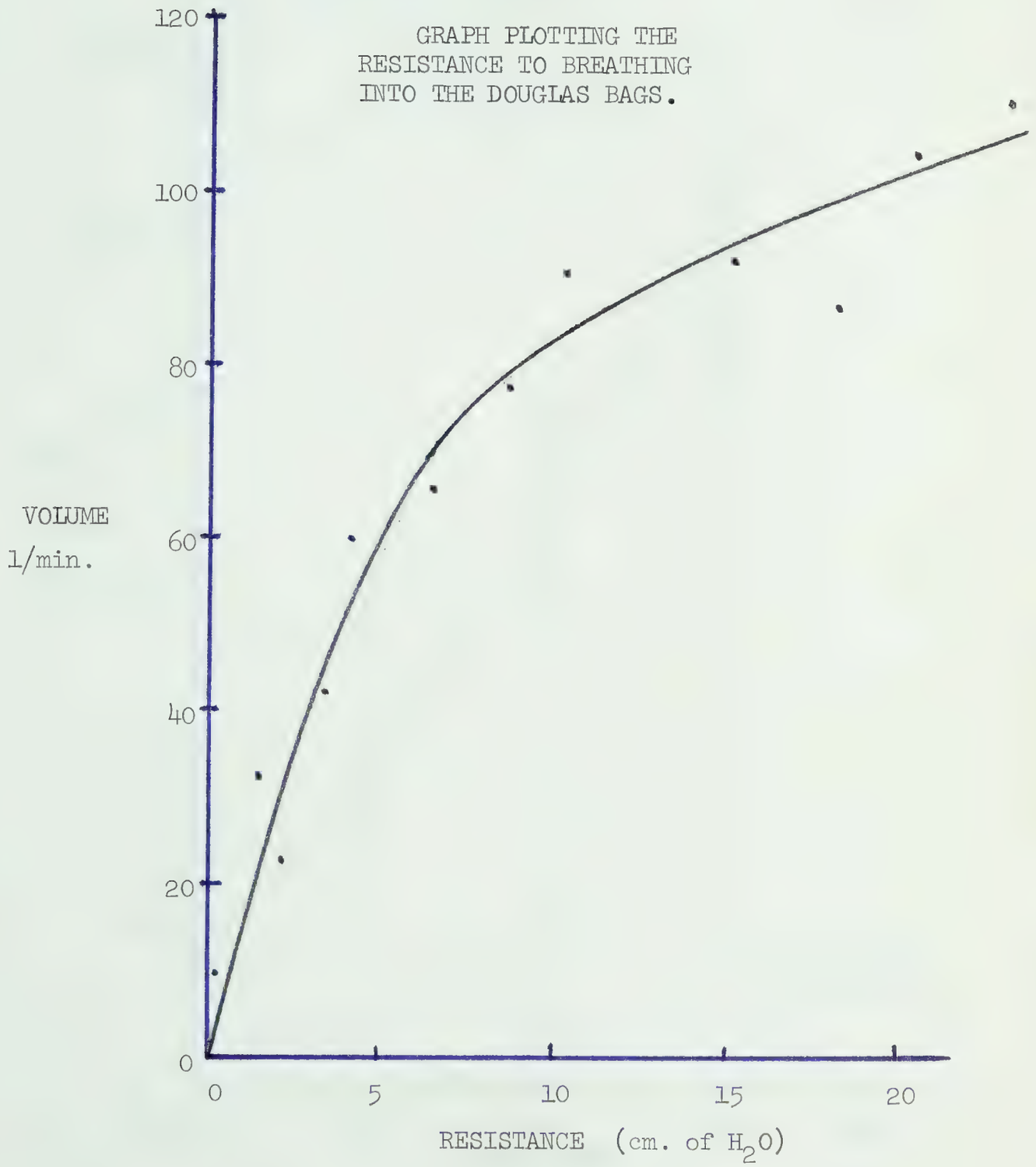

GRAPH PLOTTING THE
RESISTANCE TO BREATHING
INTO THE DOUGLAS BAGS.
VOLUME
l/min.
120
100
80
60
40
20
0
0
5
10
15
20
RESISTANCE (cm. of H_2O)

Figure 5

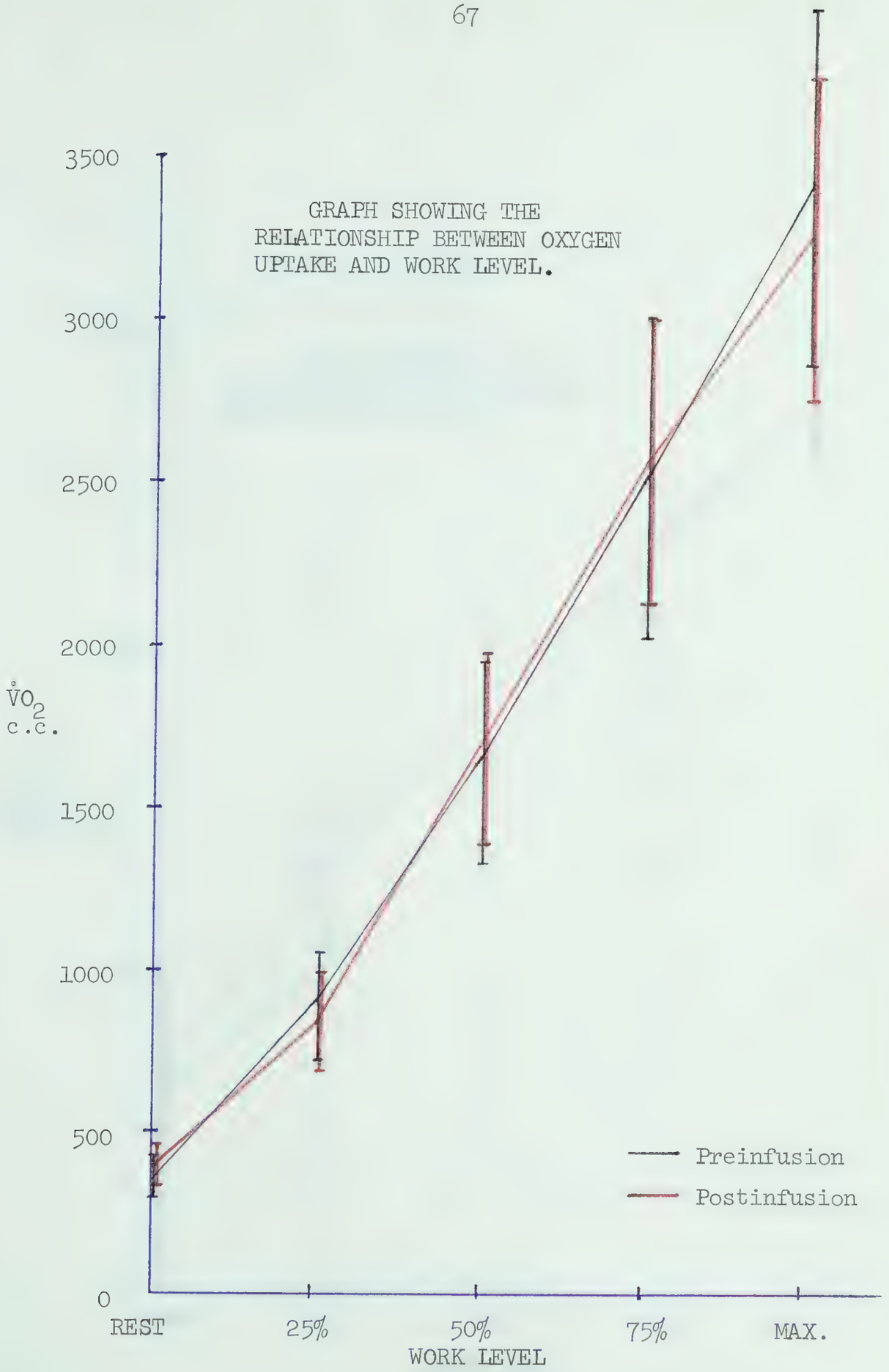

GRAPH SHOWING THE
RELATIONSHIP BETWEEN OXYGEN
UPTAKE AND WORK LEVEL.
3500
3000
2500
2000
1500
1000
500
0
$\dot{V}O_2$
c.c.
REST
25%
50%
75%
MAX.
WORK LEVEL
Preinfusion
Postinfusion

Figure 6

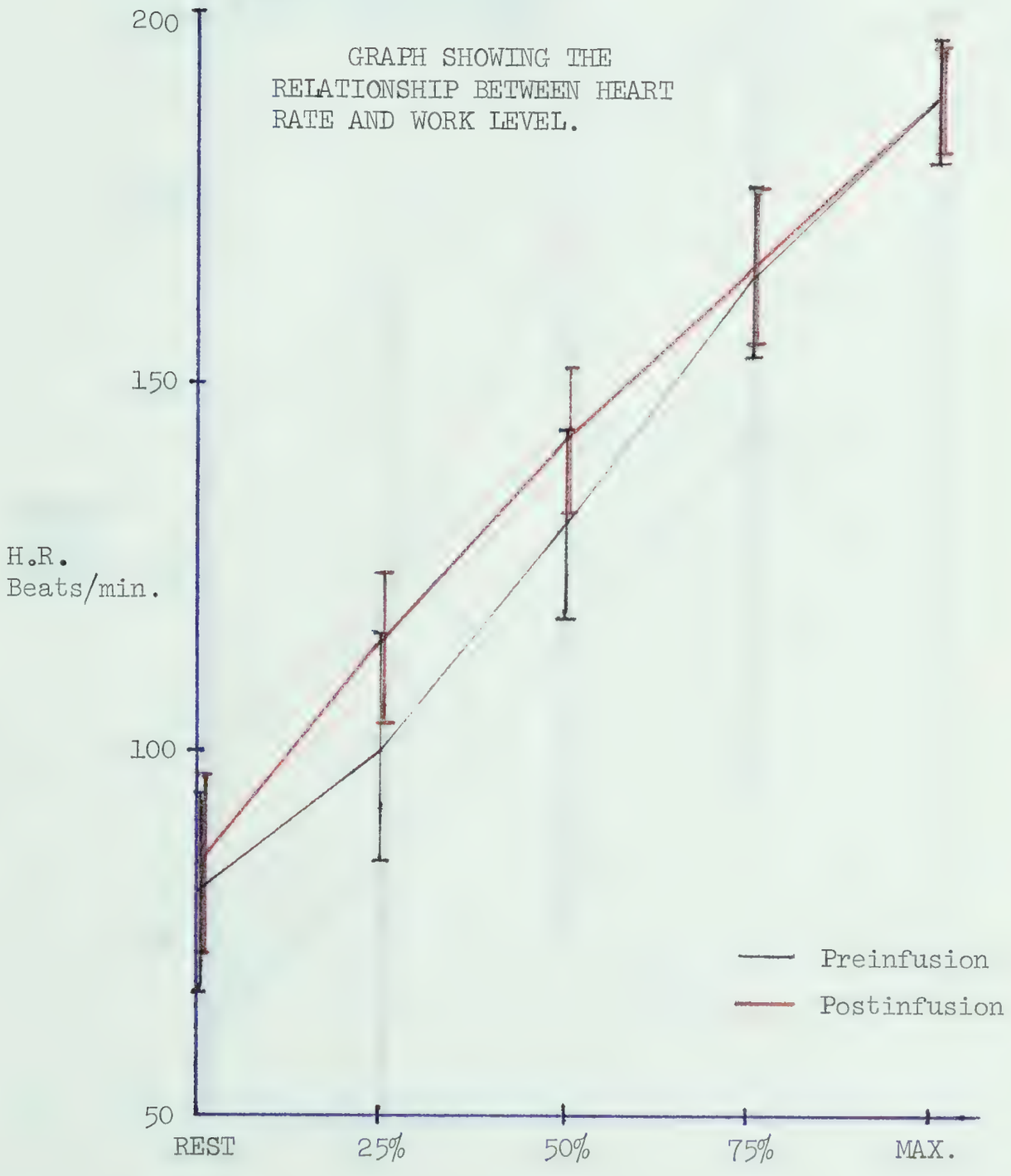

GRAPH SHOWING THE
RELATIONSHIP BETWEEN HEART
RATE AND WORK LEVEL.
200
150
100
50
H.R.
Beats/min.
Preinfusion
Postinfusion
REST
25%
50%
75%
MAX.
WORK LEVEL

Figure 7

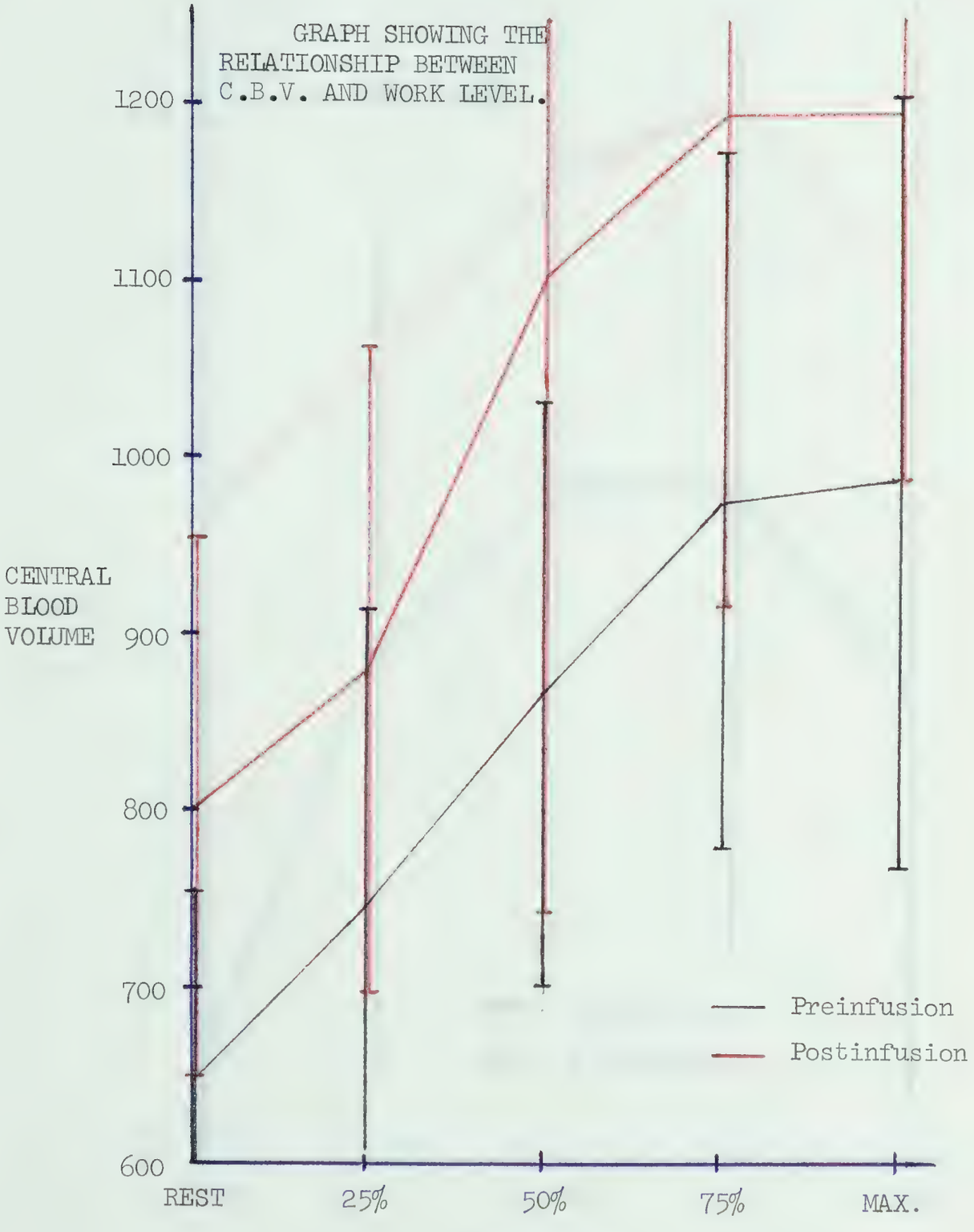

GRAPH SHOWING THE
RELATIONSHIP BETWEEN
C.B.V. AND WORK LEVEL.
1200
1100
1000
900
800
700
600
CENTRAL
BLOOD
VOLUME
Preinfusion
Postinfusion
REST
25%
50%
75%
MAX.
WORK LEVEL

Figure 8

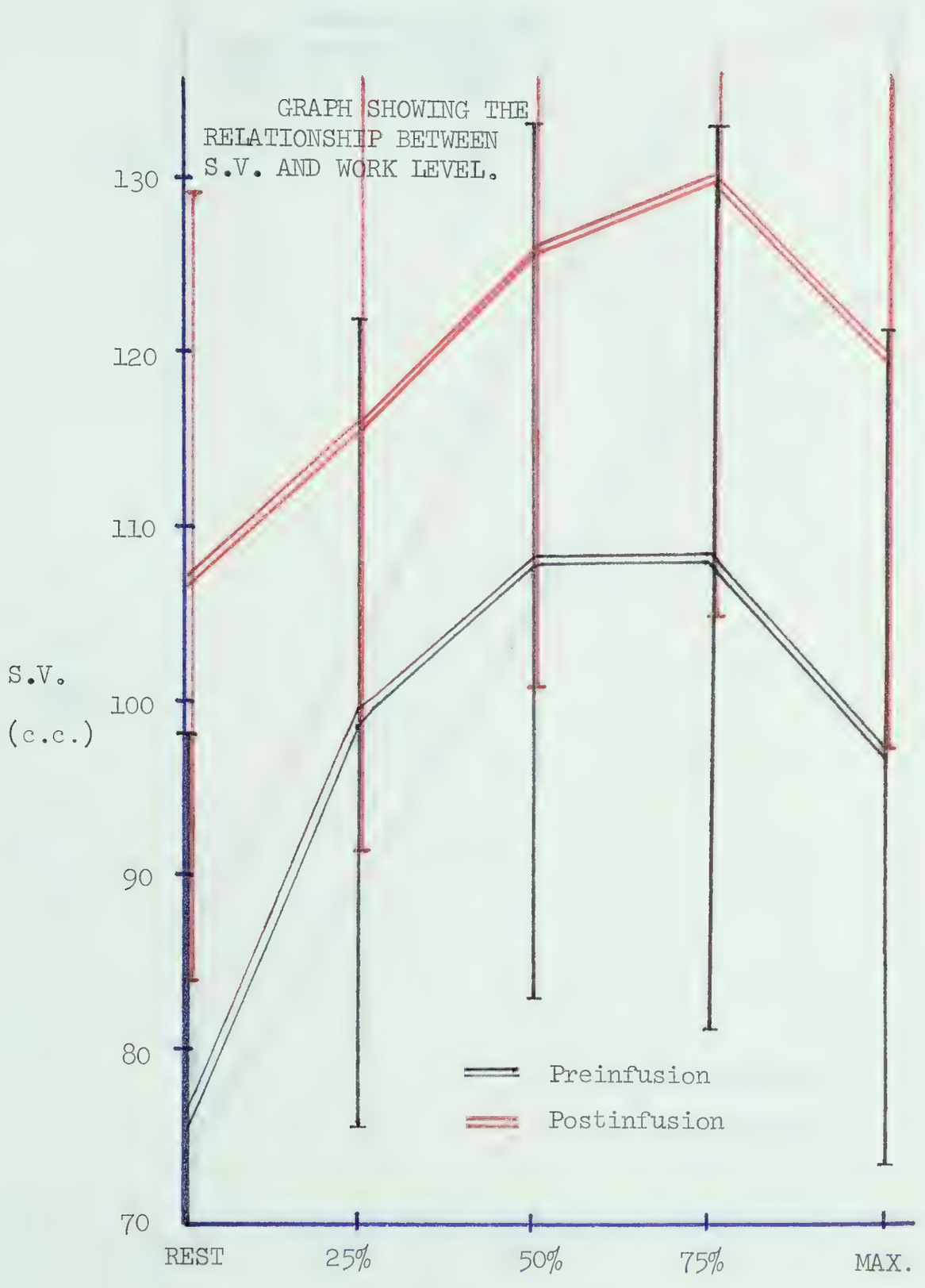

GRAPH SHOWING THE
RELATIONSHIP BETWEEN
S.V. AND WORK LEVEL.
130
120
110
100
90
80
70
S.V.
(c.c.)
Preinfusion
Postinfusion
REST
25%
50%
75%
MAX.
WORK LEVEL

Figure 9

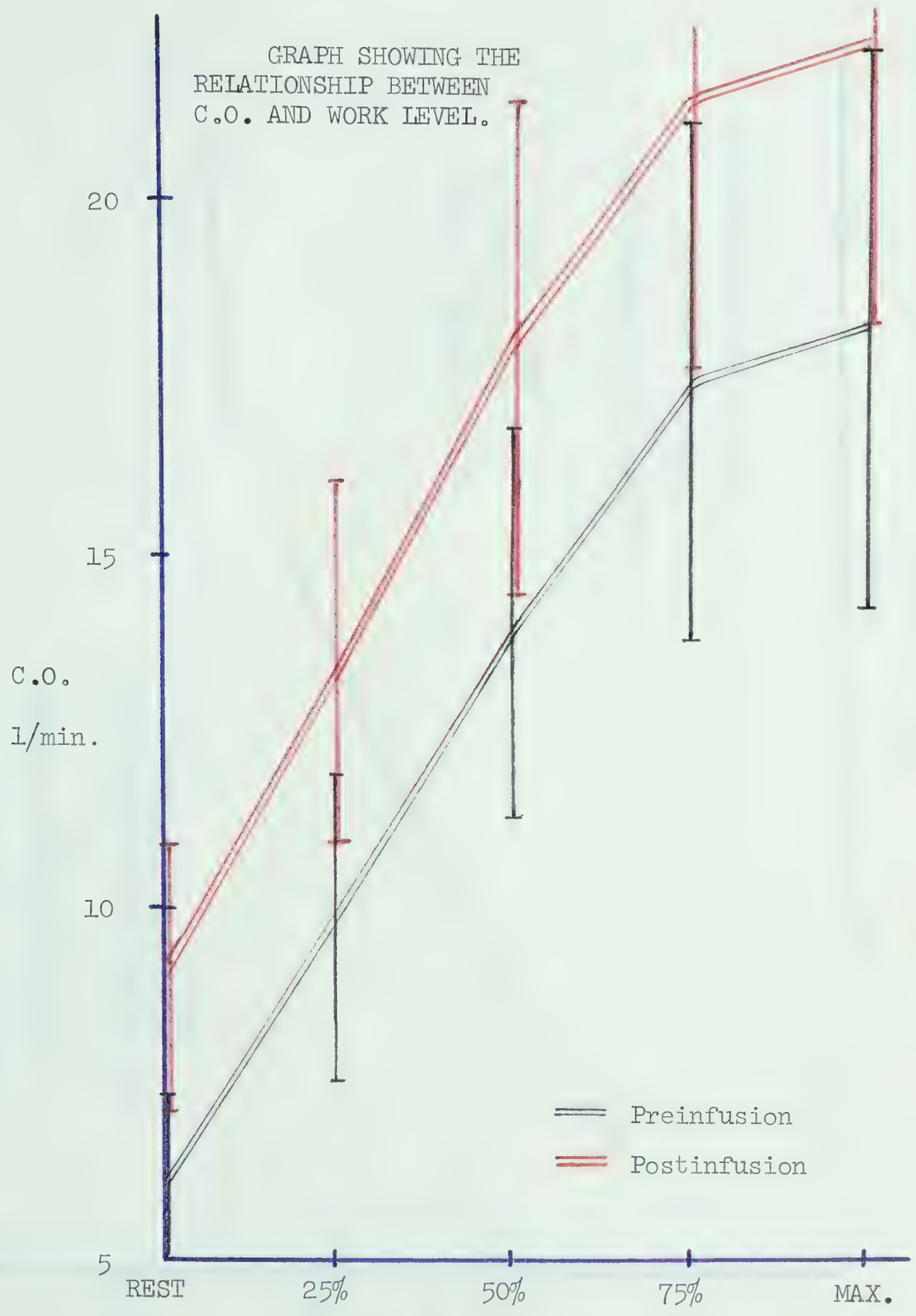

GRAPH SHOWING THE
RELATIONSHIP BETWEEN
C.O. AND WORK LEVEL.
20
15
10
5
C.O.
l/min.
Preinfusion
Postinfusion
REST
25%
50%
75%
MAX.
WORK LEVEL

Figure 10

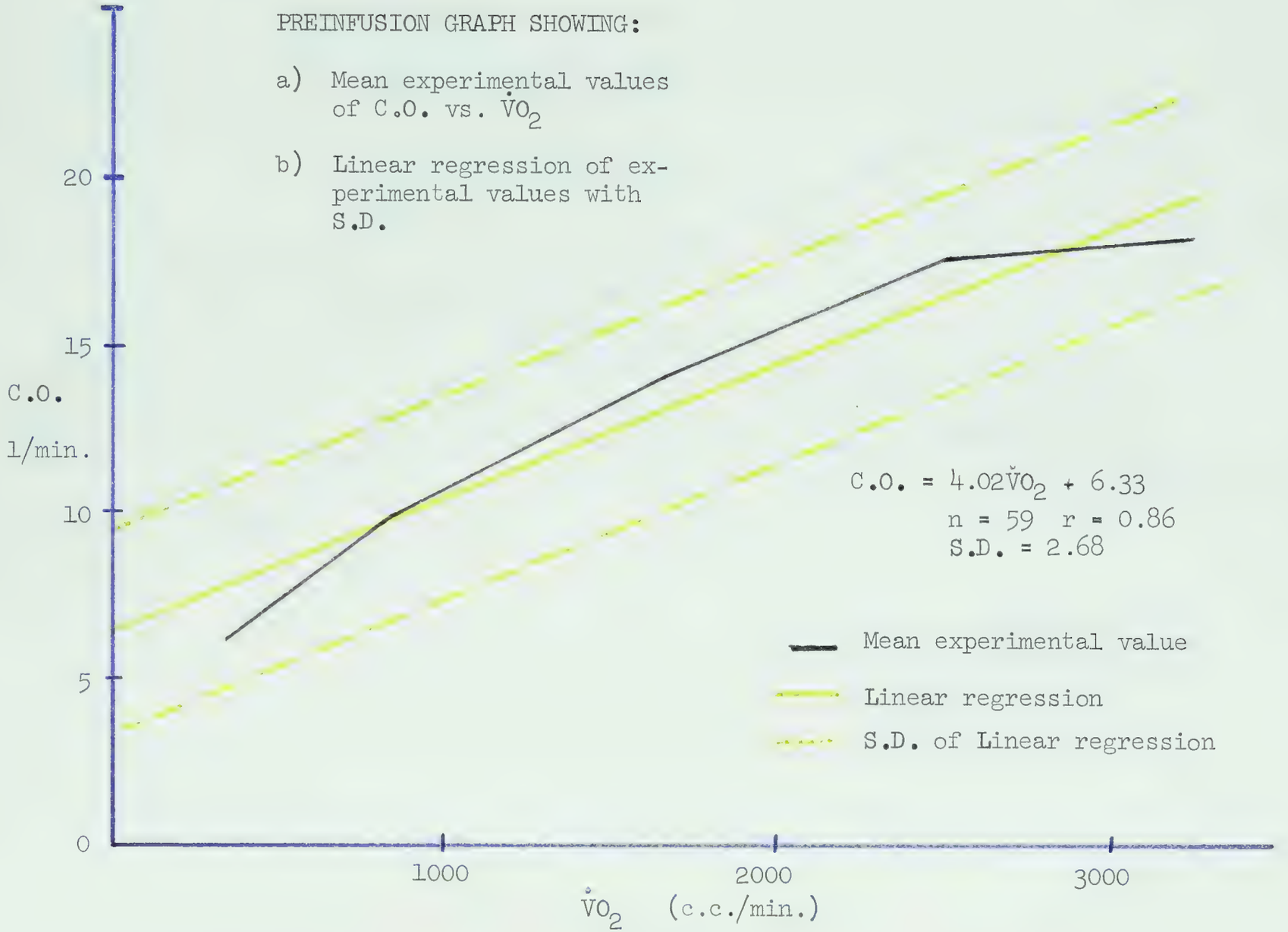

PREINFUSION GRAPH SHOWING:
a) Mean experimental values of C.O. vs. $\dot{V}O_2$
b) Linear regression of experimental values with S.D.
C.O. l/min.
20
15
10
5
0
1000
2000
3000
$\dot{V}O_2$ (c.c./min.)
C.O. = 4.02$\dot{V}O_2$ + 6.33
n = 59 r = 0.86
S.D. = 2.68
Mean experimental value
Linear regression
S.D. of Linear regression

Figure 11

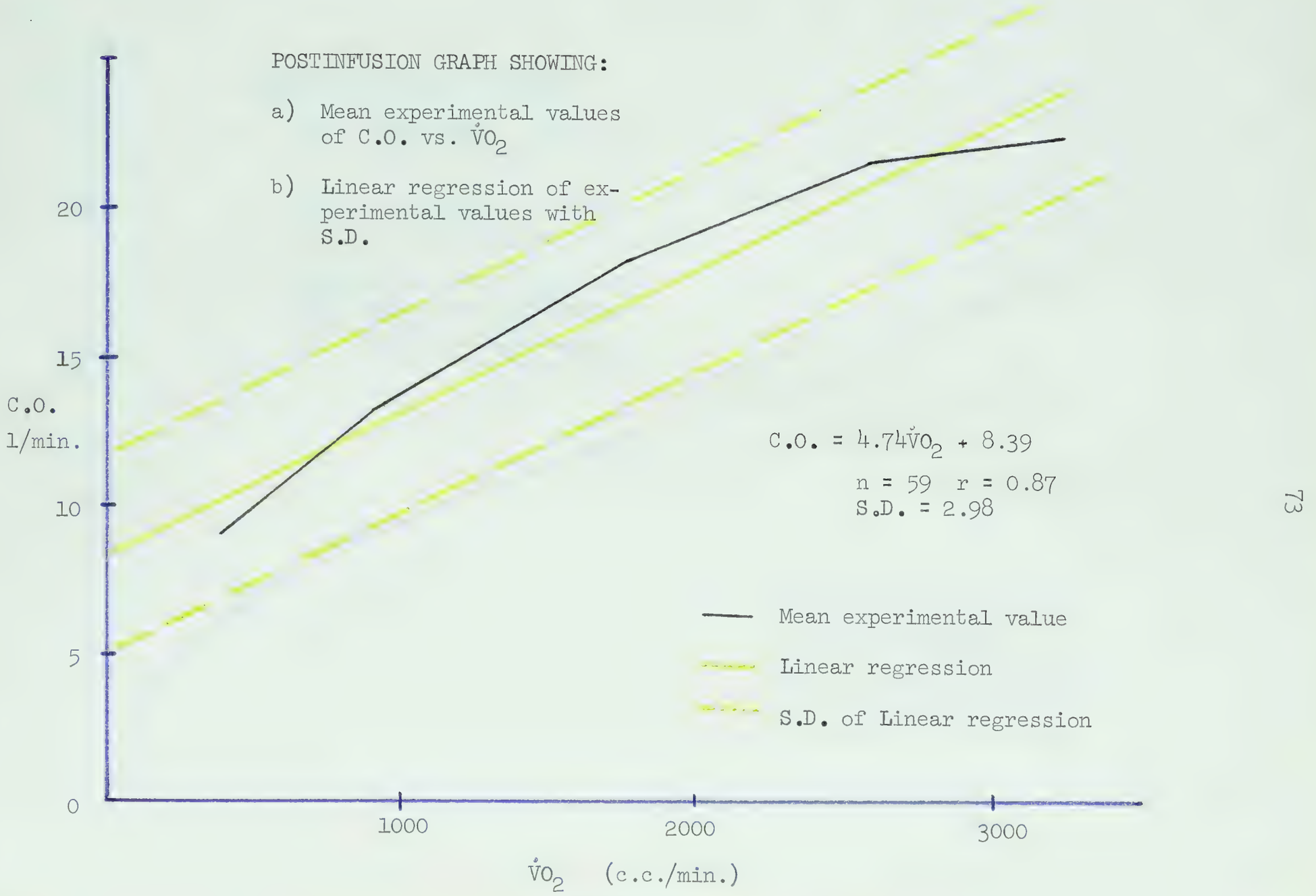

POSTINFUSION GRAPH SHOWING:
a) Mean experimental values of C.O. vs. $\dot{V}O_2$
b) Linear regression of experimental values with S.D.
C.O. = 4.74$\dot{V}O_2$ + 8.39
n = 59 r = 0.87
S.D. = 2.98
Mean experimental value
Linear regression
S.D. of Linear regression
C.O. l/min.
0
5
10
15
20
1000
2000
3000
$\dot{V}O_2$ (c.c./min.)

Figure 12

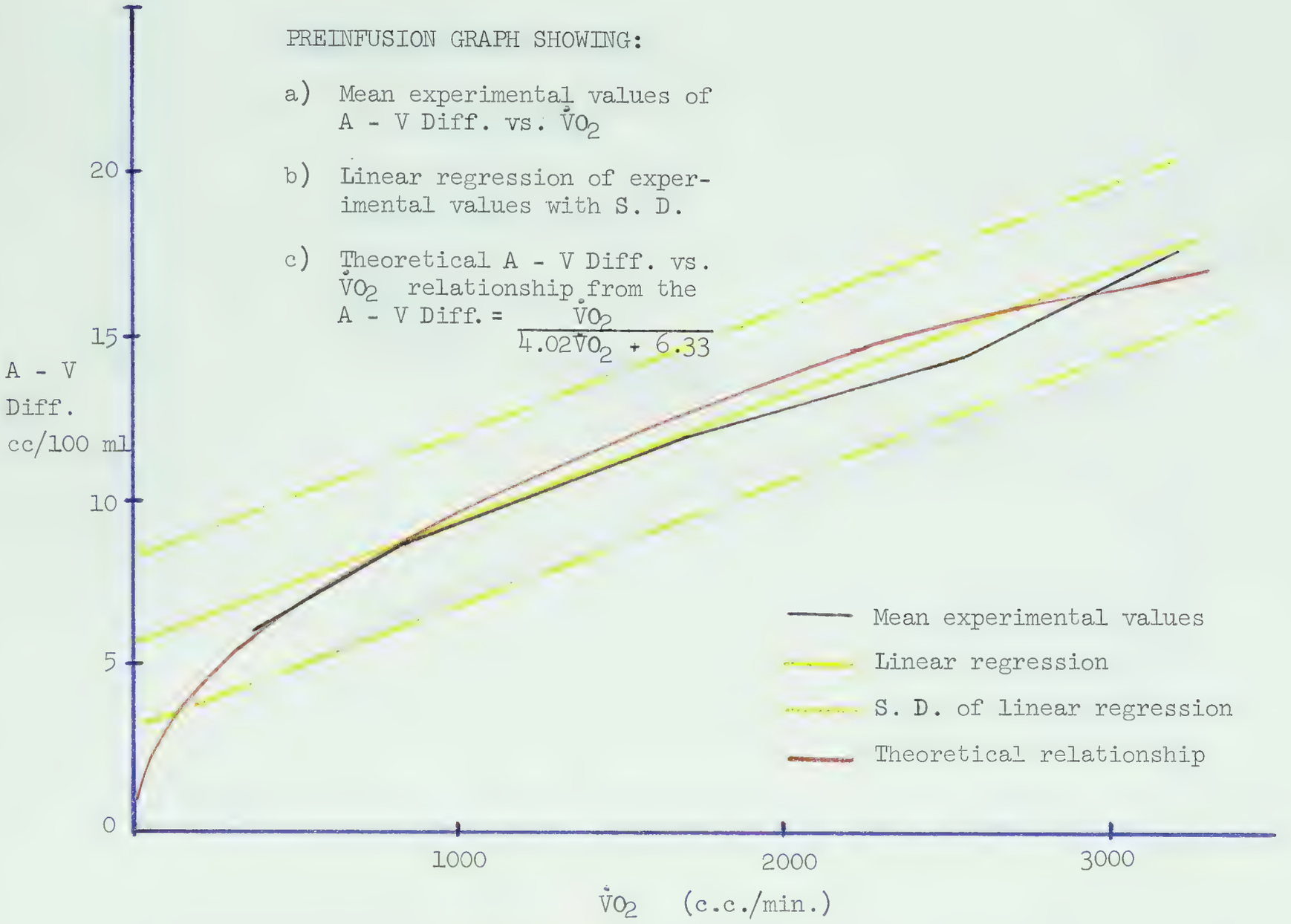

PREINFUSION GRAPH SHOWING:
a) Mean experimental values of A - V Diff. vs. $\dot{V}O_2$
b) Linear regression of experimental values with S. D.
c) Theoretical A - V Diff. vs. $\dot{V}O_2$ relationship from the A - V Diff. = $\frac{\dot{V}O_2}{4.02\dot{V}O_2 + 6.33}$
A - V Diff. cc/100 ml
20
15
10
5
0
1000
2000
3000
$\dot{V}O_2$ (c.c./min.)
Mean experimental values
Linear regression
S. D. of linear regression
Theoretical relationship

Figure 13

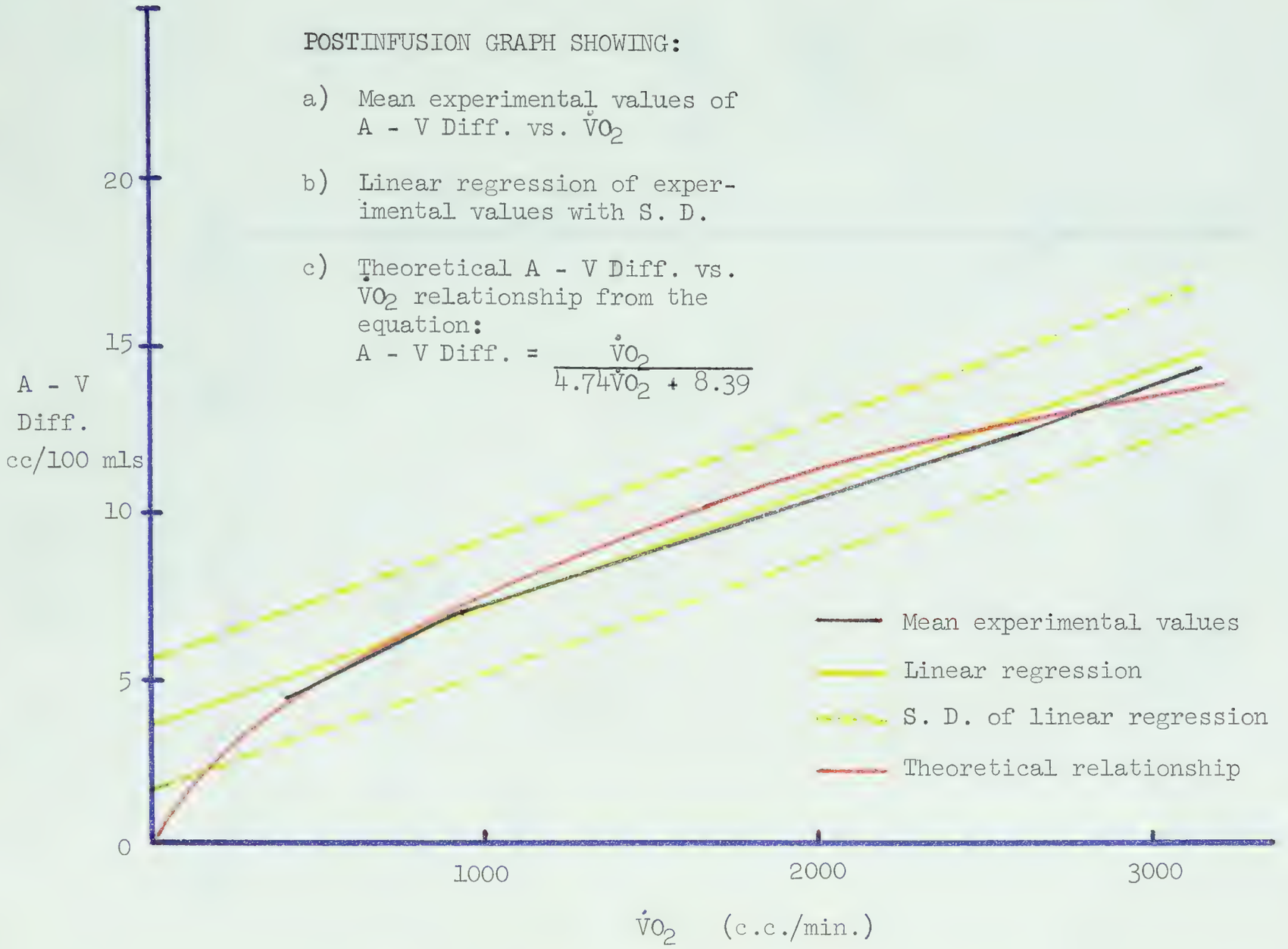

POSTINFUSION GRAPH SHOWING:
a) Mean experimental values of A - V Diff. vs. $\dot{V}O_2$
b) Linear regression of experimental values with S. D.
c) Theoretical A - V Diff. vs. $\dot{V}O_2$ relationship from the equation:
A - V Diff. = $\frac{\dot{V}O_2}{4.74\dot{V}O_2 + 8.39}$
A - V Diff. cc/100 mls
0
5
10
15
20
1000
2000
3000
$\dot{V}O_2$ (c.c./min.)
Mean experimental values
Linear regression
S. D. of linear regression
Theoretical relationship

Figure 14

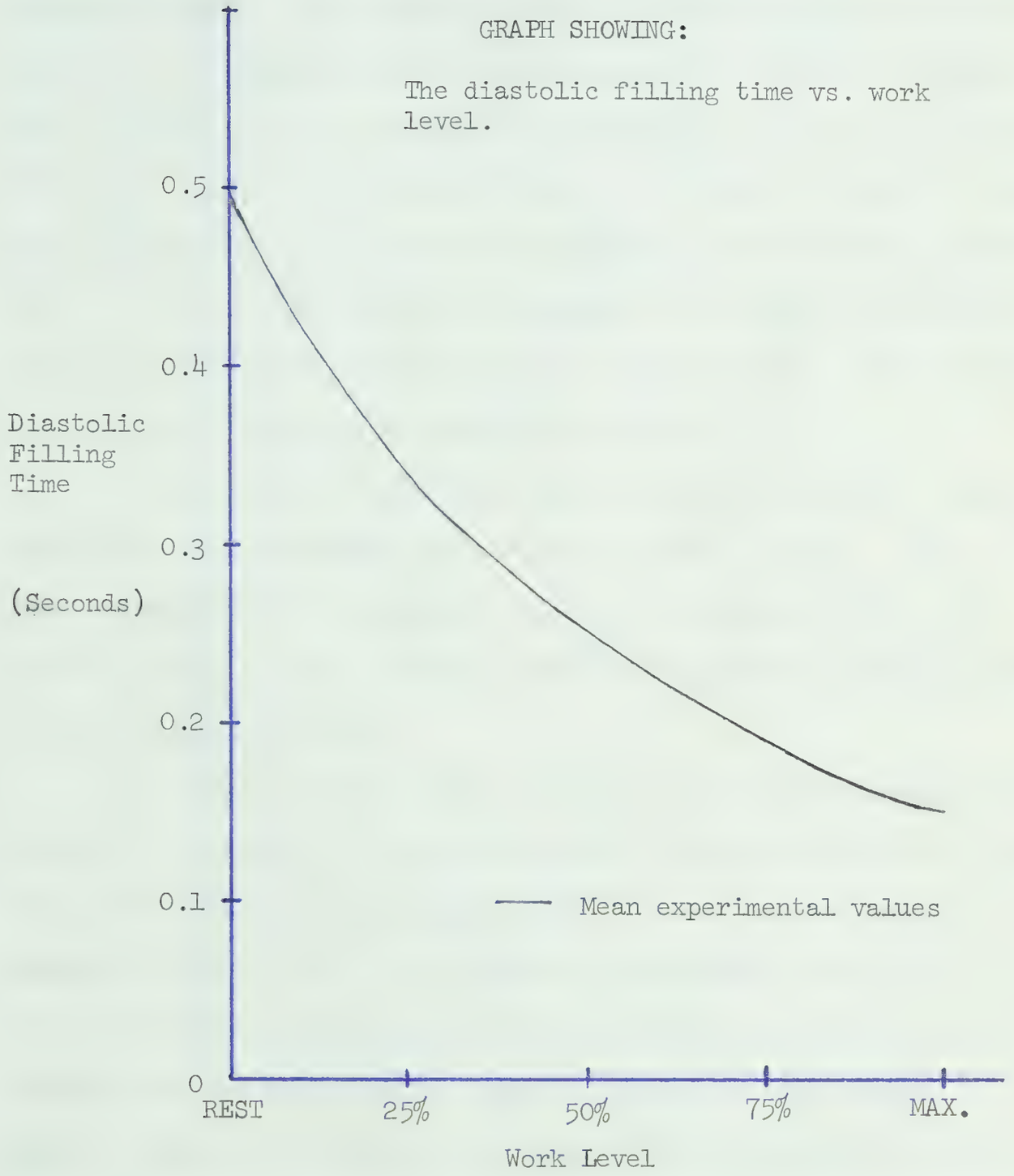

GRAPH SHOWING:
The diastolic filling time vs. work level.
0.5
0.4
0.3
0.2
0.1
0
Diastolic Filling Time
(Seconds)
Mean experimental values
REST
25%
50%
75%
MAX.
Work Level

Figure 15

SUMMARY AND CONCLUSIONS

(I) A significant increase in cardiac output (stroke volume) was found at rest and at all levels of exercise including the maximal after dextran infusion. The observed increase in cardiac output was attributed to the significant reduction of peripheral resistance (about 20%). This decrease in P.V.R. with dextran infusion, which was noted at rest and at all levels of exercise, is due to the reduced Hb. and Hct. (12% and 10% respectively) as well as dilatation of the resistance vessels.

(II) Stroke volume reached a maximum at the 50% and 75% work level, then decreased significantly at the maximal exertion level. This was noted in both the preinfusion and postinfusion study.

Stroke volume was found to be a parabolic function of heart rate, mean right atrial pressure and the mean systemic pressure. All of these variables have an optimum value which is reached before the maximal cardiac output. Dextran infusion increases the optimal values of S.V., H.R., and $R.A.\bar{p}$.

The reduced stroke volume during maximal exercise appears to be due to a combination of functions (i.e. decreased diastolic filling time and the right atrial pressure). At maximal cardiac output the diastolic filling time drops to about 0.15 seconds, which does not appear to be sufficient time to adequately fill the ventricle and end-diastolic volume falls with a resulting fall in stroke volume.

(III) Central blood volume increased with exercise linearly up to the 75% of maximum exercise. However, no further increase was found during maximum exercise. This would indicate that the pulmonary vasculature

undergoes a progressive dilatation during exercise - reaching a maximum at the 75% level of exercise.

(IV) The cardiac output versus oxygen uptake relationship increases linearly in the submaximal region (to 75% of the maximal exercise level) but falls off at maximal and resting values. This has been shown by other authors.

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